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International application number: PCT/GB05/000498

International filing date: 11 February 2005 (11.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0403155.5
Filing date: 12 February 2004 (12.02.2004)

Date of receipt at the International Bureau: 08 April 2005 (08.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

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12 FEB 2004

Patents ADP number *(if you know it)* 7915184001

If the applicant is a corporate body, give the country/state of its incorporation — **UNITED KINGDOM**

4. Title of the invention — **CHEMICAL COMPOUNDS**

5. Name of your agent *(if you have one)* — **Carpmaels & Ransford**

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Signature: Carpmaels & Ransford — Date: **12th February 2004**

12. Name and daytime telephone number of person to contact in the United Kingdom: **Dr. B.R. Cockerton** **020-7242 8692**

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CHEMICAL COMPOUNDS

The present invention relates to pyrimidine-4-carboxamide derivatives and their use in therapy. In particular, the present invention relates to the treatment of disorders in which the reduction of purinergic neurotransmission could be beneficial. The invention relates in particular to blockade of adenosine receptors and particularly adenosine A_{2A} receptors, and to the treatment of movement disorders such as Parkinson's disease.

Movement disorders constitute a serious health problem, especially amongst the elderly sector of the population. These movement disorders are often the result of brain lesions. Disorders involving the basal ganglia which result in movement disorders include Parkinson's disease, Huntington's chorea and Wilson's disease. Furthermore, dyskinesias often arise as sequelae of cerebral ischaemia and other neurological disorders.

There are four classic symptoms of Parkinson's disease: tremor, rigidity, akinesia and postural changes. The disease is also commonly associated with depression, dementia and overall cognitive decline. Parkinson's disease has a prevalence of 1 per 1,000 of the total population. The incidence increases to 1 per 100 for those aged over 60 years. Degeneration of dopaminergic neurones in the substantia nigra and the subsequent reductions in interstitial concentrations of dopamine in the striatum are critical to the development of Parkinson's disease. Some 80% of cells from the substantia nigra need to be destroyed before the clinical symptoms of Parkinson's disease are manifested.

Current strategies for the treatment of Parkinson's disease are based on transmitter replacement therapy (L-dihydroxyphenylacetic acid (L-DOPA)), inhibition of monoamine oxidase (e.g. Deprenyl®), dopamine receptor agonists (e.g. bromocriptine and apomorphine) and anticholinergics (e.g. benztrophine, orphenadrine). Transmitter replacement therapy in particular does not provide consistent clinical benefit, especially after prolonged treatment when "on-off" symptoms develop, and this treatment has also been associated with involuntary movements of athetosis and chorea, nausea and vomiting. Additionally current therapies do not treat the underlying neurodegenerative disorder resulting in a continuing cognitive decline in patients. Despite new drug approvals, there is still a medical need in terms of improved therapies for movement disorders, especially

Parkinson's disease. In particular, effective treatments requiring less frequent dosing, effective treatments which are associated with less severe side-effects, and effective treatments which control or reverse the underlying neurodegenerative disorder, are required.

Blockade of A_2 adenosine receptors has recently been implicated in the treatment of movement disorders such as Parkinson's disease (Richardson, P.J. *et al.*, *Trends Pharmacol. Sci.* 1997, 18, 338-344) and in the treatment of cerebral ischaemia (Gao, Y. and Phillis, J.W., *Life Sci.* 1994, 55, 61-65). The potential utility of adenosine A_{2A} receptor antagonists in the treatment of movement disorders such as Parkinson's Disease has recently been reviewed (Mally, J. and Stone, T.W., *CNS Drugs*, 1998, 10, 311-320).

Adenosine is a naturally occurring purine nucleoside which has a wide variety of well-documented regulatory functions and physiological effects. The central nervous system (CNS) effects of this endogenous nucleoside have attracted particular attention in drug discovery, owing to the therapeutic potential of purinergic agents in CNS disorders (Jacobson, K.A. *et al.*, *J. Med. Chem.* 1992, 35, 407-422). This therapeutic potential has resulted in considerable recent research endeavour within the field of adenosine receptor agonists and antagonists (Bhagwhat, S.S.; Williams, M. *Exp. Opin. Ther. Patents* 1995, 5,547-558).

Adenosine receptors represent a subclass (P_1) of the group of purine nucleotide and nucleoside receptors known as purinoreceptors. The main pharmacologically distinct adenosine receptor subtypes are known as A_1, A_{2A}, A_{2B} (of high and low affinity) and A_3 (Fredholm, B.B., *et al.*, *Pharmacol. Rev.* 1994, 46, 143-156). The adenosine receptors are present in the CNS (Fredholm, B.B., *News Physiol. Sci.*, 1995, 10, 122-128).

The design of P_1 receptor-mediated agents has been reviewed (Jacobson, K.A., Suzuki, F., *Drug Dev. Res.*, 1997, 39, 289-300; Baraldi, P.G. *et al.*, *Curr. Med. Chem.* 1995, 2, 707-722), and such compounds are claimed to be useful in the treatment of cerebral ischemia or neurodegenerative disorders, such as Parkinson's disease (Williams, M. and Burnstock, G. *Purinergic Approaches Exp. Ther.* (1997), 3-26. Editor: Jacobson, Kenneth A.; Jarvis, Michael F. Publisher: Wiley-Liss, New York, N.Y.)

It has been speculated that xanthine derivatives such as caffeine may offer a form of treatment for attention-deficit hyperactivity disorder (ADHD). A number of studies have demonstrated a beneficial effect of caffeine on controlling the symptoms of ADHD (Garfinkel, B.D. *et al., Psychiatry*, 1981, **26**, 395-401). Antagonism of adenosine receptors is thought to account for the majority of the behavioural effects of caffeine in humans and thus blockade of adenosine A_{2A} receptors may account for the observed effects of caffeine in ADHD patients. Therefore a selective A_{2A} receptor antagonist may provide an effective treatment for ADHD but without the unwanted side-effects associated with current therapy.

Adenosine receptors have been recognised to play an important role in regulation of sleep patterns, and indeed adenosine antagonists such as caffeine exert potent stimulant effects and can be used to prolong wakefulness (Porkka-Heiskanen, T. *et al., Science,* 1997, **276,** 1265-1268). Recent evidence suggests that a substantial part of the actions of adenosine in regulating sleep is mediated through the adenosine A_{2A} receptor (Satoh, S., *et al., Proc. Natl. Acad. Sci.,* USA, 1996). Thus, a selective A_{2A} receptor antagonist may be of benefit in counteracting excessive sleepiness in sleep disorders such as hypersomnia or narcolepsy.

It has recently been observed that patients with major depression demonstrate a blunted response to adenosine agonist-induced stimulation in platelets, suggesting that a dysregulation of A_{2A} receptor function may occur during depression (Berk, M. et al, 2001, *Eur. Neuropsychopharmacol.* 11, 183-186). Experimental evidence in animal models has shown that blockade of A_{2A} receptor function confers antidepressant activity (El Yacoubi, M et al. *Br. J. Pharmacol.* 2001, 134, 68-77). Thus, A_{2A} receptor antagonists may offer a novel therapy for the treatment of major depression and other affective disorders in patients.

The pharmacology of adenosine A_{2A} receptors has been reviewed (Ongini, E.; Fredholm, B.B. *Trends Pharmacol. Sci.* 1996, 17(10), 364-372). One potential underlying mechanism in the aforementioned treatment of movement disorders by the blockade of A_2 adenosine receptors is the evidence of a functional link between adenosine A_{2A} receptors to dopamine D_2 receptors in the CNS. Some of the early studies (e.g. Ferre, S. *et al.*, Stimulation of high-affinity adenosine A_2 receptors decreases the affinity of dopamine D_2

receptors in rat striatal membranes. *Proc. Natl. Acad. Sci.* U.S.A. 1991, 88, 7238-41) have been summarised in two more recent articles (Fuxe, K. *et al., Adenosine Adenine Nucleotides Mol. Biol. Integr. Physiol.*, [Proc. Int. Symp.], 5th (1995), 499-507. Editors: Belardinelli, Luiz; Pelleg, Amir. Publisher: Kluwer, Boston, Mass.; Ferre, S. *et al., Trends Neurosci.* 1997, 20, 482-487).

As a result of these investigations into the functional role of adenosine A_{2A} receptors in the CNS, especially *in vivo* studies linking A_2 receptors with catalepsy (Ferre *et al., Neurosci. Lett.* 1991, 130, 162-4; Mandhane, S.N. *et al., Eur. J. Pharmacol.* 1997, 328, 135-141) investigations have been made into agents which selectively bind to adenosine A_{2A} receptors as potentially effective treatments for Parkinson's disease.

While many of the potential drugs for treatment of Parkinson's disease have shown benefit in the treatment of movement disorders, an advantage of adenosine A_{2A} antagonist therapy is that the underlying neurodegenerative disorder may also be treated. The neuroprotective effect of adenosine A_{2A} antagonists has been reviewed (Ongini, E.; Adami, M.; Ferri, C.; Bertorelli, R., *Ann. N. Y. Acad. Sci.* 1997, 825(Neuroprotective Agents), 30-48). In particular, compelling recent evidence suggests that blockade of A_{2A} receptor function confers neuroprotection against MPTP-induced neurotoxicity in mice (Chen, J-F., *J. Neurosci.* 2001, 21, RC143). In addition, several recent studies have shown that consumption of dietary caffeine, a known adenosine A_{2A} receptor antagonist, is associated with a reduced risk of Parkinson's disease in man (Ascherio, A. et al, *Ann Neurol.*, 2001, 50, 56-63; Ross G W, et al., *JAMA*, 2000, 283, 2674-9). Thus, A_{2A} receptor antagonists may offer a novel treatment for conferring neuroprotection in neurodegenerative diseases such as Parkinson's disease.

Xanthine derivatives have been disclosed as adenosine A_2 receptor antagonists as useful for treating various diseases caused by hyperfunctioning of adenosine A_2 receptors, such as Parkinson's disease (see, for example, EP-A-565377).

One prominent xanthine-derived adenosine A_{2A} selective antagonist is CSC [8-(3-chlorostyryl)caffeine] (Jacobson *et al., FEBS Lett.*, 1993, 323, 141-144).

Theophylline (1,3-dimethylxanthine), a bronchodilator drug which is a mixed antagonist at adenosine A_1 and A_{2A} receptors, has been studied clinically. To determine whether a formulation of this adenosine receptor antagonist would be of value in Parkinson's disease an open trial was conducted on 15 Parkinsonian patients, treated for up to 12 weeks with a slow release oral theophylline preparation (150 mg/day), yielding serum theophylline levels of 4.44 mg/L after one week. The patients exhibited significant improvements in mean objective disability scores and 11 reported moderate or marked subjective improvement (Mally, J., Stone, T.W. *J. Pharm. Pharmacol.* 1994, 46, 515-517).

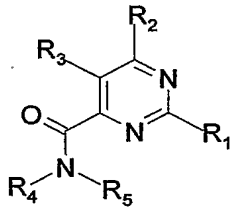
KF 17837 [(E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine] is a selective adenosine A_{2A} receptor antagonist which on oral administration significantly ameliorated the cataleptic responses induced by intracerebroventricular administration of an adenosine A_{2A} receptor agonist, CGS 21680. KF 17837 also reduced the catalepsy induced by haloperidol and reserpine. Moreover, KF 17837 potentiated the anticataleptic effects of a subthreshold dose of L-DOPA plus benserazide, suggesting that KF 17837 is a centrally active adenosine A_{2A} receptor antagonist and that the dopaminergic function of the nigrostriatal pathway is potentiated by adenosine A_{2A} receptor antagonists (Kanda, T. *et al., Eur. J. Pharmacol.* 1994, 256, 263-268). The structure activity relationship (SAR) of KF 17837 has been published (Shimada, J. *et al., Bioorg. Med. Chem. Lett.* 1997, 7, 2349-2352). Recent data has also been provided on the A_{2A} receptor antagonist KW-6002 (Kuwana, Y *et al., Soc. Neurosci. Abstr.* 1997, 23, 119.14; and Kanda, T. *et al., Ann. Neurol.* 1998, 43(4), 507-513).

New non-xanthine structures sharing these pharmacological properties include SCH 58261 and its derivatives (Baraldi, P.G. *et al.*, Pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine Derivatives: Potent and Selective A_{2A} Adenosine Antagonists. *J. Med. Chem.* 1996, 39, 1164-71). SCH 58261 (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-e]-1,2,4-triazolo[1,5-c] pyrimidine) is reported as effective in the treatment of movement disorders (Ongini, E. *Drug Dev. Res.* 1997, 42(2), 63-70) and has been followed up by a later series of compounds (Baraldi, P.G. *et al., J. Med. Chem.* 1998, 41(12), 2126-2133). WO-A-01/62233 discloses a series of cyclic heteroaromatic compounds containing at least one nitrogen atom and their use as adenosine receptor modulators. FR-2201083 discloses a series of phenylpyrimidines with analgesic activity.

The foregoing discussion indicates that a potentially effective treatment for movement disorders in humans would comprise agents which act as antagonists at adenosine A_{2A} receptors.

It has now been found that the pyrimidine-4-carboxamide derivatives described herein, which are structurally unrelated to known adenosine receptor antagonists, exhibit unexpected antagonist binding affinity at adenosine (P_1) receptors, and in particular at the adenosine A_{2A} receptor. Such compounds may therefore be useful for the treatment of disorders in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors, is beneficial, for instance movement disorders, such as disorders of the basal ganglia which result in dyskinesias.

According to the present invention there is provided the use of a compound of formula (1):



(I)

wherein

R_1 is selected from H, alkyl, NR_6R_7, OR_8, SR_9 and halogen;

R_2 is selected from aryl and heteroaryl attached via a carbon atom;

R_3 is selected from H, alkyl, halogen, OH and OR_{10};

R_4 is selected from H, alkyl, aryl and heteroaryl,

R_5 is selected from H and alkyl;

or R_4 and R_5 together form a 5 or 6-membered heterocyclic ring;

R_6 and R_7 are independently selected from H and alkyl; and

R_8, R_9 and R_{10} are independently selected from alkyl;

and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors, is beneficial.

As used herein the term "alkyl", unless otherwise stated, means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical which may be substituted or unsubstituted. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and iso-pentyl), more preferably methyl. It will be appreciated therefore that the term "alkyl" as used herein, unless otherwise stated, includes alkyl (branched or unbranched), alkenyl (branched or unbranched), alkynyl (branched or unbranched), cycloalkyl, cycloalkenyl and cycloalkynyl. In particular, the term "alkyl" refers to an acyclic, saturated hydrocarbyl radical.

As used herein, the term "lower alkyl" means an acyclic C_1, C_2, C_3 or C_4 hydrocarbyl radical, particularly a saturated acyclic C_1, C_2, C_3 or C_4 hydrocarbyl radical, and particularly selected from methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl).

The term "aryl", as used herein as a group or part of a group, denotes: (i) an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety (preferably monocyclic) of from 6 to 14 carbon atoms, preferably from 6 to 10 carbon atoms, such as phenyl or naphthyl, and in one embodiment preferably phenyl; or (ii) an optionally substituted bicyclic structure formed by an aromatic carbocyclic moiety fused to a saturated or partially saturated carbocyclic moiety, for instance a phenyl and a C_{5-7} cycloalkyl or C_{5-7} cycloalkenyl group fused together, to form groups such as tetrahydronaphthyl, indenyl or indanyl; or (iii) an optionally substituted bicyclic structure formed by an aromatic carbocyclic moiety fused to a saturated or partially saturated heterocycloalkyl moiety, for instance a phenyl ring and a C_{5-7} heterocycloalkyl or fused together, to form groups such as benzodioxinyl. Embodiment (i) is preferred. The aryl group may be substituted by one or more substituent groups.

The term "heteroaryl", as used herein as a group or part of a group, denotes: (i) an optionally substituted heteroaromatic monocyclic or multicyclic organic moiety of from 5 to 14 ring atoms, preferably from 5 to 10 ring atoms, in which one or more of the ring atoms is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur, and

examples of such groups are pyridyl, pyrrolyl, quinolinyl, furanyl, thienyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, pyrimidinyl, indolyl, pyrazinyl, indazolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzofuranyl, benzothienyl, indolizinyl, isoquinolinyl, isothiazolyl, pyridazinyl, and quinazolinyl; and groups; (ii) an optionally substituted multicyclic moiety in which a heteroaryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure (examples of such groups include pyrindanyl groups). Embodiment (i) is preferred. The heteroaryl group may be substituted by one or more substituent groups.

As used herein, the term "non-aromatic heterocyclyl" means a non-aromatic cyclic group containing one or more heteroatom(s) preferably selected from N, O and S, such as a cyclic amino group (including aziridinyl, azetidinyl, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl) or a cyclic ether (including tetrahydrofuranyl).

As used herein, the terms "ortho-substituted" and "ortho,ortho-disubstituted", when applied to aryl or heteroaryl groups, refer to aryl or heteroaryl groups which are substituted in one or both ortho positions, respectively, of the aromatic ring relative to the point of attachment of the aromatic ring to the pyrimidine ring.

As used herein, the term "alkoxy" means alkyl-O-. As used herein, the term "aryloxy" means aryl-O-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical.

As used herein, the term "prodrug" means any pharmaceutically acceptable prodrug of a compound of the present invention. "Prodrug" means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of formula (I).

Where any of R_1 to R_{18} is selected from alkyl, in accordance with formula (I) as defined herein, then that alkyl group may be substituted or unsubstituted. Where R_2 or R_4 , R_{13} and R_{15} to R_{18} are selected from aryl and heteroaryl, in accordance with formula (I) as defined herein, then said aryl group may be substituted or unsubstituted. Where any of R_1 to R_{18} is

selected from alkyl substituted with aryl or heteroaryl, i.e. where any of R_1 to R_{18} is arylalkyl or heteroarylalkyl, the aryl or heteroaryl group may be substituted or unsubstituted. Where R_4 and R_5, or R_{15} and R_{16}, are linked to form a 5 or 6-membered heterocyclic ring, said heterocyclic ring may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent.

Substituent groups are selected from:

carbon-containing groups such as

- alkyl,
- aryl, (e.g. substituted and unsubstituted phenyl (including (alkyl)phenyl, (alkoxy)phenyl, (alkyl- and aryl-sulfonylamino)phenyl and halophenyl),
- heteroaryl,

halogen atoms and halogen containing groups such as

- haloalkyl (e.g. trifluoromethyl),
- haloaryl (e.g. chlorophenyl);

oxygen containing groups such as

- alcohols (e.g. hydroxy, hydroxyalkyl, hydroxyaryl, (aryl)(hydroxy)alkyl),
- ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl, alkoxyaryl, aryloxyaryl),
- aldehydes (e.g. carboxaldehyde),
- ketones (e.g. alkylcarbonyl, arylcarbonyl, alkylcarbonylalkyl, alkylcarbonylaryl, arylcarbonylalkyl, arylcarbonylaryl, arylalkylcarbonyl, arylalkylcarbonylalkyl, arylalkylcarbonylaryl)
- acids (e.g. carboxy, carboxyalkyl, carboxyaryl),
- acid derivatives such as esters (e.g. alkoxycarbonyl, aryloxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonylalkyl, alkoxycarbonylaryl, aryloxycarbonylaryl, alkylcarbonyloxy, alkylcarbonyloxyalkyl),
- amides

(e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, cyclicaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl or arylalkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino or arylalkylcarbonylamino),

carbamates

(eg. alkoxycarbonylamino, aryloxycarbonylamino, arylalkyloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylaminocarbonyloxy or arylalkylaminocarbonyloxy)

and ureas

(eg. mono- or di-alkylaminocarbonylamino, arylaminocarbonylamino or arylalkylaminocarbonylamino);

nitrogen containing groups such as

amines (e.g. amino, mono- or dialkylamino, cyclicamino, arylamino, aminoalkyl, mono- or dialkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro,

sulfonamides (e.g. aminosulfonyl, mono- or di-alkylaminosulfonyl, mono- or di-arylaminosulfonyl, alkyl- or aryl-sulfonylamino, alkyl- or aryl-sulfonyl(alkyl)amino, alkyl- or aryl-sulfonyl(aryl)amino);

sulfur containing groups such as

thiols, thioethers, sulfoxides, and sulfones

(e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

silicon containing groups such as

silyl (e.g. trialkylsilyl);

and heterocyclic groups containing one or more, preferably one, heteroatom,

(e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

Preferred substituent groups are selected from halogen, hydroxy, alkoxy, amino, amido, alkyl, substituted alkyl (including haloalkyl (particularly CF_3), hydroxyalkyl, alkoxyalkyl, amidoalkyl, aminoalkyl and alkylcarbamate), aryl (preferably phenyl), heteroaryl, nitro, cyano and carbamate.

In the compounds of formula (I), R_1 is selected from H, alkyl (including haloalkyl), NR_6R_7, OR_8, SR_9 and halogen. Preferably, R_1 is selected from NR_6R_7, OR_8, SR_9 and halogen, preferably from NR_6R_7, OR_8 and SR_9, and more preferably from NR_6R_7. Where R_1 is selected from NR_6R_7, preferably at least one and preferably both of R_6 and R_7 are selected from H.

In the compounds of formula (I), R_2 is selected from aryl and heteroaryl attached via a carbon atom, including substituted aryl and heteroaryl. Preferably R_2 is a monocyclic group. Preferably R_2 is not ortho,ortho-disubstituted, and is preferably not ortho-substituted. Preferably, R_2 is selected from heteroaryl, preferably containing one or more heteroatom(s) selected from O, S and N atoms, preferably wherein said heteroatom(s) are adjacent the carbon atom which is attached to the pyrimidine ring.

When R_2 is heteroaryl, R_2 is preferably selected from furyl (preferably 2-furyl), thienyl (preferably 2-thienyl), thiazolyl (preferably 2-thiazolyl), oxazolyl (preferably 2-oxazolyl), imidazolyl (preferably 2-imidazolyl) and pyridyl (preferably 2-pyridyl), more preferably from furyl (preferably 2-furyl) and thiazolyl (preferably 2-thiazolyl), and preferably R_2 is furyl, preferably 2-furyl.

In the embodiment where R_2 is aryl, particularly phenyl, R_5 is preferably selected from H or forms a heterocyclic ring with R_4, and is preferably H. In this embodiment, R_4 is preferably selected from H, alkyl, heteroaryl and substituted alkyl (particularly arylalkyl and heteroarylalkyl) or forms a heterocyclic ring with R_5, more preferably R_4 is selected from H, heteroaryl and substituted alkyl (particularly arylalkyl and heteroarylalkyl) or forms a heterocyclic ring with R_5, more preferably R_4 is selected from heteroaryl and substituted alkyl (particularly arylalkyl and heteroarylalkyl) or forms a heterocyclic ring with R_5, and more preferably R_4 is selected from heteroaryl and substituted alkyl (particularly arylalkyl and heteroarylalkyl). In this embodiment, where R_4 is alkyl, then the alkyl group preferably contains at least 2 carbon atoms. In this embodiment, the R_2 group may be substituted or unsubstituted.

In the compounds of formula (I), R_3 is selected from H, alkyl (including haloalkyl), halogen, OH and OR_{10}, and preferably from H, alkyl (including haloalkyl) and halogen, more preferably from H and alkyl (including haloalkyl), and more preferably from H and lower alkyl (optionally substituted, particularly with halogen).

In the compounds of formula (I), R_4 is selected from H, alkyl (including substituted alkyl, particularly arylalkyl and heteroarylalkyl), aryl and heteroaryl, or together with R_5 forms a 5 or 6-membered heterocyclic ring. Preferably R_4 is selected from alkyl (including substituted alkyl, particularly arylalkyl and heteroarylalkyl), aryl and heteroaryl, or together with R_5 forms a 5 or 6-membered heterocyclic ring. Preferably R_4 is selected from alkyl (including substituted alkyl, particularly arylalkyl and heteroarylalkyl), aryl and heteroaryl. Preferably R_4 is selected from substituted alkyl, particularly arylalkyl and heteroarylalkyl, particularly wherein said alkyl is lower alkyl, particularly methyl.

In the embodiment where R_4 is selected from substituted alkyl, R_4 is preferably selected from a group of formula (II):

$$-(CR_{11}R_{12})_n-A \qquad (II)$$

wherein

R_{11} and R_{12} are independently selected from hydrogen and alkyl (preferably lower alkyl), and preferably from H;

n is selected from 1, 2, 3 and 4, preferably from 1, 2 and 3, more preferably from 1 and 2, and preferably n is 1; and

A is selected from aryl and heteroaryl, as defined herein.

In formula II where A is aryl, the aryl group is preferably monocyclic and preferably phenyl. In formula II where A is heteroaryl, the heteroaryl group may particularly be selected from furyl, pyridyl, thienyl, pyrazolyl, thiazolyl, oxazolyl, imidazolyl, pyrimidinyl, pyrollyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl and benzothiadiazolyl, and in one embodiment is monocyclic.

In a preferred embodiment, the group A in formula II is substituted by one or more substituent groups R_A. Typically, only one substituent group R_A is present. The group(s) R_A is/are selected from the substituent groups referred to herein, and particularly from halogen, R_{13}, OR_{14}, and $NR_{15}R_{16}$; wherein:

R_{13} is selected from alkyl, aryl and heteroaryl;

R_{14} is selected from alkyl (preferably lower alkyl); and

where R_{15} and R_{16} are independently selected from H, alkyl (preferably lower alkyl), aryl and heteroaryl, and preferably from H and alkyl; or R_{15} and R_{16} together form a 5 or 6-membered heterocyclic ring wherein said heterocyclic ring may be saturated, partially unsaturated or aromatic, and is preferably saturated, and wherein said heterocyclic ring may contain one or more additional heteroatom(s) preferably selected from N, O and S, and in one embodiment contains no further heteroatoms, and in one embodiment is unsubstituted.

In one embodiment R_A is selected from $-(CH_2)p-X$, wherein:

p is selected from 1, 2, 3 or 4, preferably from 1, 2 or 3, preferably from 1 or 2, and is preferably 1; and

X is selected from OH, -OR_{14}, -$NR_{15}R_{16}$, -$OCONR_{15}R_{16}$ and -$NR_{17}COR_{18}$; wherein
R_{14}, R_{15} and R_{16} are as defined above; and
R_{17} and R_{18} are independently selected from H, alkyl (preferably lower alkyl), aryl and heteroaryl, and preferably from H and alkyl (preferably lower alkyl).

In the compounds of formula (I), R_5 is selected from H and alkyl, or together with R_4 forms a 5 or 6-membered heterocyclic ring. R_5 is preferably H.

Where R_4 and R_5 are linked to form a 5 or 6-membered heterocyclic ring, said heterocyclic ring may be saturated, partially unsaturated or aromatic, and is preferably saturated. Said heterocyclic ring may contain one or more additional heteroatom(s) preferably selected from N, O and S. In one embodiment, the heterocyclic ring contains no further heteroatoms. In one embodiment, the heterocyclic ring is unsubstituted. In one embodiment, the 5 or 6-membered heterocyclic ring may be fused to an aromatic ring system, particularly a monocyclic ring system (preferably containing 6 ring atoms, such as phenyl) to form a multicyclic moiety, such as dihydroindolyl, dihydroisoindolyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl.

In the compounds of formula (I), R_6 and R_7 are independently selected from H and alkyl, and preferably from H. Preferably both R_6 and R_7 are selected from H. Where R_6 and R_7 are selected from alkyl, the alkyl group is preferably a lower alkyl group.

In the compounds of formula (I), R_8, R_9 and R_{10} are independently selected from alkyl, preferably from lower alkyl.

Where chiral the compounds of formula (I) may be in the form of a racemic mixture of pairs of enantiomers or in enantiomerically pure form.

According to a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof, *per se*, other than compounds wherein R_2 is selected from pyrazolopyridines. In this aspect of the invention, preferably R_2 is selected as described hereinabove.

According to a further aspect of the invention, there is provided for use in therapy a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, other than compounds wherein R_2 is selected from pyrazolopyridines. In this aspect of the invention, preferably R_2 is selected as described hereinabove.

According to a further aspect of the present invention there is provided a method of treating or preventing a disorder in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors, is beneficial, the method comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof.

The disorder may be caused by the hyperfunctioning of the purine receptors.

The present invention may be employed in respect of a human or animal subject, more preferably a mammal, more preferably a human subject.

The disorders of particular interest are those in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors, may be beneficial. These may include movement disorders such as Parkinson's disease, drug-induced Parkinsonism, post-encephalitic Parkinsonism, Parkinsonism induced by poisoning (for example MPTP, manganese, carbon monoxide) and post-traumatic Parkinson's disease (punch-drunk syndrome).

Other movement disorders in which the blocking of purine receptors, may be of benefit include progressive supernuclear palsy, Huntingtons disease, multiple system atrophy, corticobasal degeneration, Wilsons disease, Hallerrorden-Spatz disease, progressive pallidal atrophy, Dopa-responsive dystonia-Parkinsonism, spasticity or other disorders of the basal ganglia which result in abnormal movement or posture. The present invention may also be effective in treating Parkinson's with on-off phenomena; Parkinson's with freezing (end of dose deterioration); and Parkinson's with prominent dyskinesias.

The compounds of formula (I) may be used or administered in combination with one or more additional drugs useful in the treatment of movement disorders, such as L-DOPA or a

dopamine agonist, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

Other disorders in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors may be beneficial include acute and chronic pain; for example neuropathic pain, cancer pain, trigeminal neuralgia, migraine and other conditions associated with cephalic pain, primary and secondary hyperalgesia, inflammatory pain, nociceptive pain, tabes dorsalis, phantom limb pain, spinal cord injury pain, central pain, post-herpetic pain and HIV pain; affective disorders including mood disorders such as bipolar disorder, seasonal affective disorder, depression, manic depression, atypical depression and monodepressive disease; central and peripheral nervous system degenerative disorders including corticobasal degeneration, demyelinating disease (multiple sclerosis, disseminated sclerosis), Freidrich's ataxia, motoneurone disease (amyotrophic lateral sclerosis, progressive bulbar atrophy), multiple system atrophy, myelopathy, radiculopathy, peripheral neuropathy (diabetic neuropathy, tabes dorsalis, drug-induced neuropathy, vitamin deficiency), systemic lupus erythamatosis, granulomatous disease, olivo-ponto-cerebellar atrophy, progressive pallidal atrophy, progressive supranuclear palsy, spasticity; schizophrenia and related psychoses; cognitive and/or memory impairment disorders including dementia, Alzheimers Disease, Frontotemporal dementia, multi-infarct dementia, AIDS dementia, dementia associated with Huntingtons Disease, Lewy body dementia, senile dementia, age-related memory impairment, cognitive impairment associated with dementia, Korsakoff syndrome, dementia pugilans; attention disorders such as attention-deficit hyperactivity disorder (ADHD), attention deficit disorder, minimal brain dysfunction, brain-injured child syndrome, hyperkinetic reaction childhood, and hyperactive child syndrome; central nervous system injury including traumatic brain injury, neurosurgery (surgical trauma), neuroprotection for head injury, raised intracranial pressure, cerebral oedema, hydrocephalus, spinal cord injury; cerebral ischaemia including transient ischaemic attack, stroke (thrombotic stroke, ischaemic stroke, embolic stroke, haemorrhagic stroke, lacunar stroke) subarachnoid haemorrhage, cerebral vasospasm, neuroprotection for stroke, peri-natal asphyxia, drowning, cardiac arrest, subdural haematoma; myocardial ischaemia; muscle ischaemia; sleep disorders such as hypersomnia, narcolepsy and restless legs syndrome; eye disorders such as retinal ischaemia-reperfusion injury and diabetic

neuropathy; cardiovascular disorders such as claudication and hypotension; and diabetes and its complications.

According to a further aspect of the present invention there is provided use of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for the treatment or prevention of movement disorders in a subject.

According to a further aspect of the invention there is provided a method of treating or preventing movement disorders comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof.

According to a further aspect of the invention there is provided use of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for neuroprotection in a subject.

According to a further aspect of the invention there is provided a method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof.

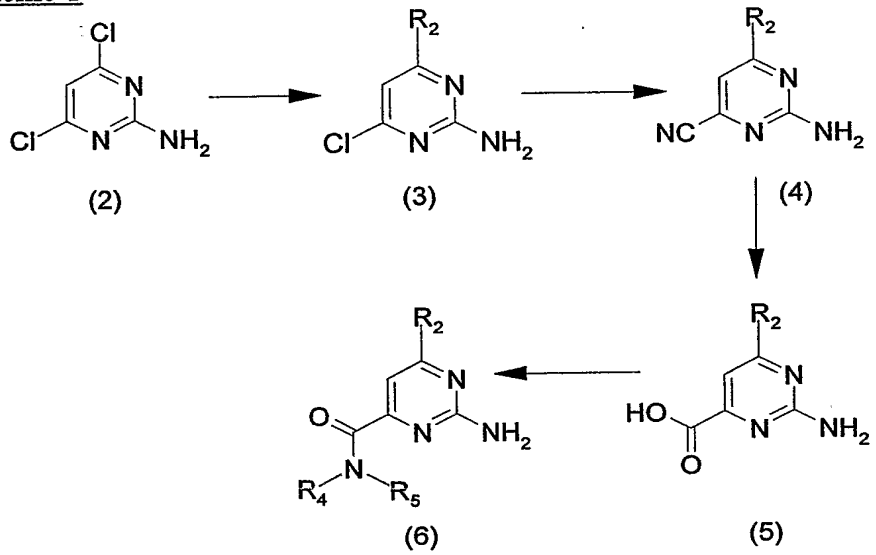
The medicament for or method of neuroprotection may be of use in the treatment of subjects who are suffering from or at risk from a neurodegenerative disorder, such as a movement disorder.

Disorders of particular interest in the present invention include movement disorders including Parkinson's disease, cognitive or memory impairment disorders including Alzheimer's disease, depression, acute or chronic pain, ADHD, narcolepsy and restless legs syndrome, and for neuroprotection.

According to a further aspect of the invention there is provided a method of preparing the novel compounds of formula (1). Compounds of formula (1) may be prepared according to

conventional synthetic methods. For example compounds of formula (1), where R_1 is NH_2, may be synthesised by standard methods such as those illustrated in Reaction Scheme 1.

Reaction Scheme 1



Compounds of formula (6) may be prepared from compounds of formula (5) by standard methods used for coupling carboxylic acids and amines. Such coupling reactions would include reaction of a carboxylic acid derivative such as an imidazolide prepared with N,N'-carbonyldiimidazole or a mixed anhydride prepared with an alkyl chloroformate and a trialkylamine base or an acyl chloride prepared from a chlorinating source such as oxalyl chloride with an appropriate amine, or by direct coupling of an appropriate amine in the presence of a standard coupling reagent such as dicyclohexylcarbodiimide and a nucleophilic catalyst such as 4-dimethylaminopyridine.

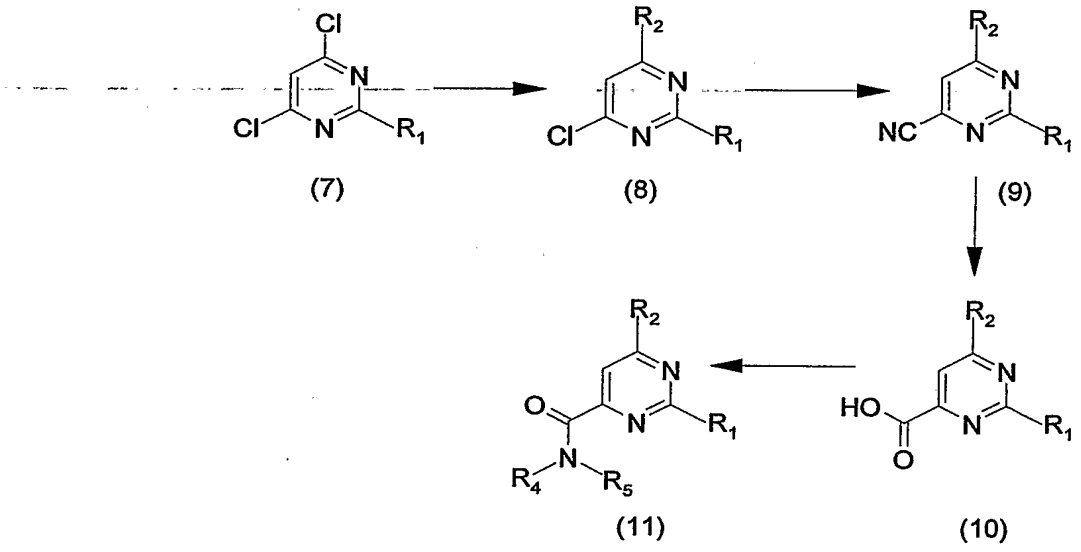
Compounds of formula (5) may be prepared from compounds of formula (4) by standard methods such as hydrolysis with a mineral acid such as sulfuric acid.

Compounds of formula (4) may be prepared from compounds of formula (3) by standard methods such as cyanation with an alkali metal cyanide such as sodium cyanide or an organic source of cyanide such as tetraethylammonium cyanide in the presence of a tertiary amine base such as 1,4-diazabicyclo[2.2.2]octane or trimethylamine.

Compounds of formula (3) are either known in the literature or may be prepared from the known compound of formula (2) by standard methods such as aryl or heteroaryl coupling reactions. Such aryl or heteroaryl coupling reactions would include reaction with an appropriate aryl or heteroarylboronic acid derivative, an aryl or heteroaryltrialkylstannane derivative or an aryl or heteroarylzinc halide derivative in the presence of a suitable catalyst such as a palladium complex.

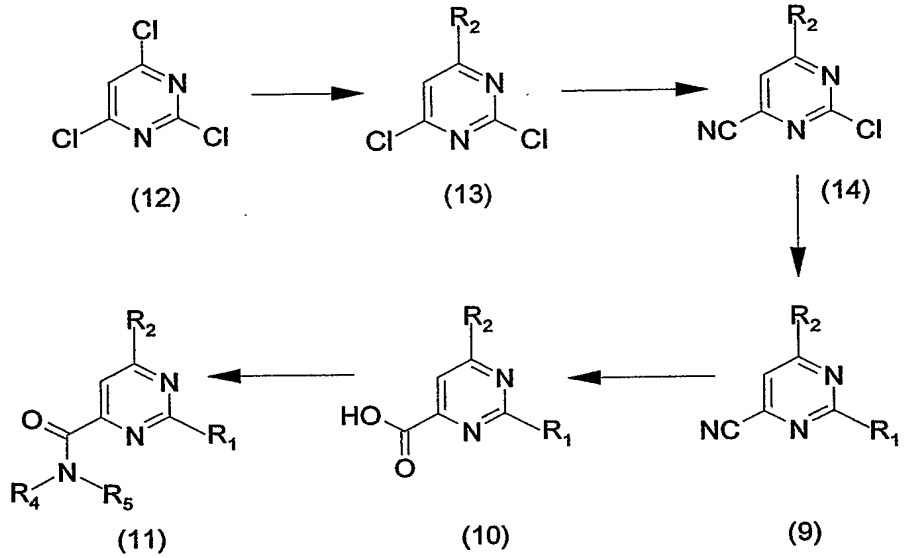
Compounds of formula (1) where R_1 is H or alkyl may be synthesised by standard methods such as those illustrated in Reaction Scheme 2.

Reaction Scheme 2



Compounds of formula (1) where R_1 is NHAlkyl, $N(Alkyl)_2$, OAlkyl or SAlkyl may be synthesised by standard methods such as those illustrated in Reaction Scheme 3.

Reaction Scheme 3



According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

The pharmaceutical compositions employed in the present invention comprise a compound of formula (I), or pharmaceutically acceptable salts or prodrugs thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients known to those skilled in the art. The term, "pharmaceutically acceptable salts", refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

Where the compounds of formula (I) are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are

hydrochloric, hydrobromic, phosphoric, and sulfuric acids, and most particularly preferred is the hydrochloride salt.

Any suitable route of administration may be employed for providing the patient with an effective dosage of a compound of formula (I). For example, oral, rectal, parenteral (intravenous, intramuscular), transdermal, subcutaneous, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like. The most suitable route in any given case will depend on the severity of the condition being treated. The most preferred route of administration of the present invention is the oral route. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practical use, the compounds of formula (I) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.* oral or parenteral (*e.g.* intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavouring agents, preservatives, colouring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used in the case of oral solid preparations such as, for example, powders, capsules, and tablets, with the solid oral preparations being preferred over the liquid preparations. The most preferred solid oral preparation is tablets.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or non-aqueous techniques.

In addition to the common dosage forms set out above, the compounds of formula (I) may also be administered by controlled release means and/or delivery devices such as those

described in United States Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200; 4,008,719; 4,687,660; and 4,769,027, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions employed in the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosol sprays each containing a predetermined amount of the active ingredient as a powder or granules, a solution or a suspension in an aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

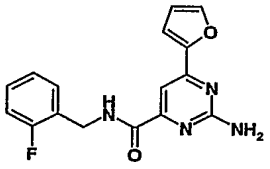
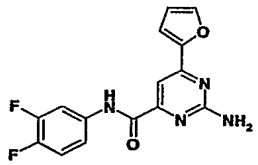
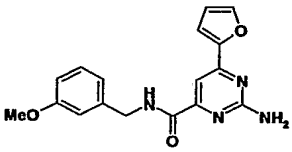
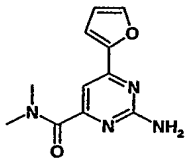
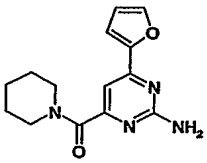
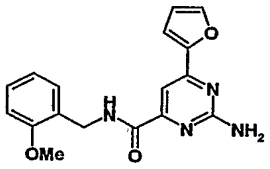
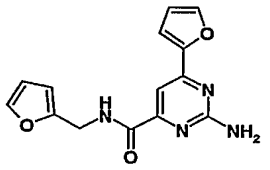
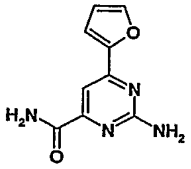
The invention is further defined by reference to the following examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practised without departing from the purpose and interest of this invention.

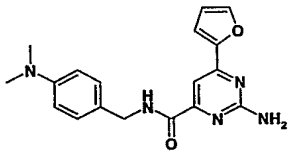
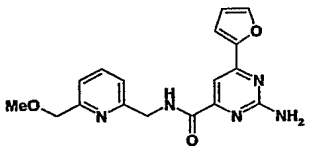
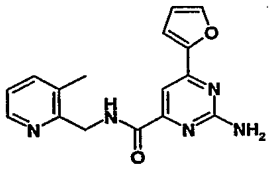
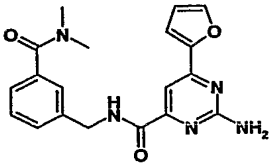
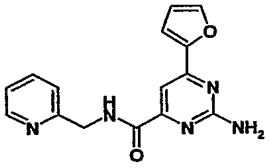
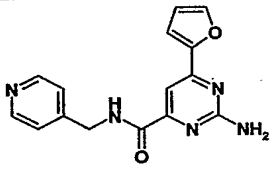
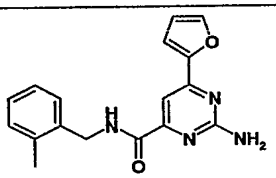
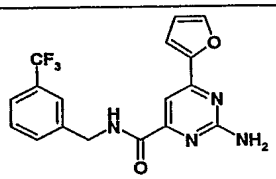
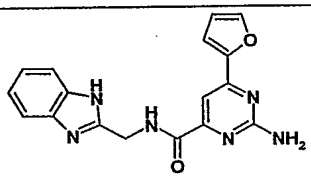
EXAMPLES

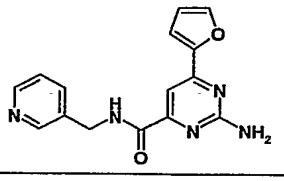
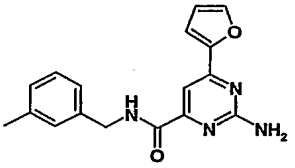
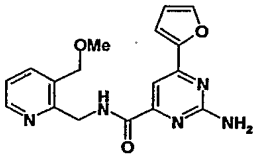
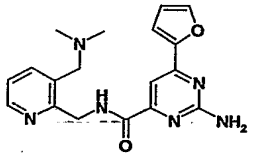
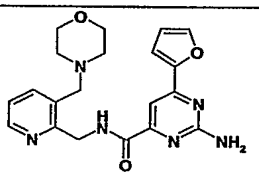
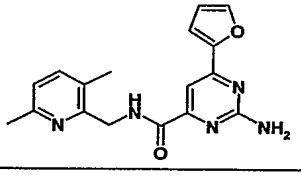
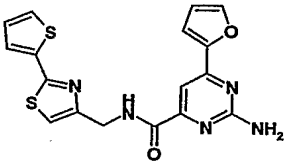
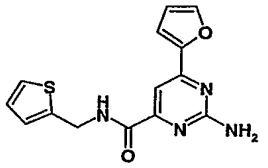
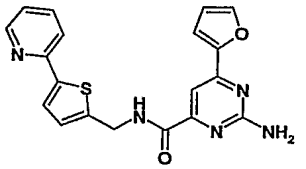
Synthetic Examples

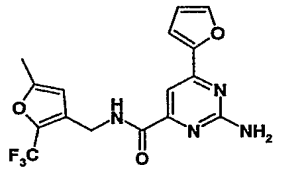
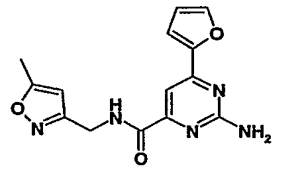
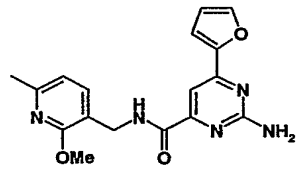
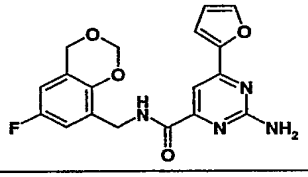
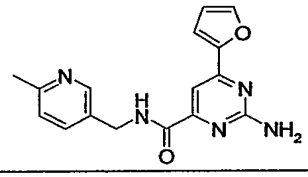
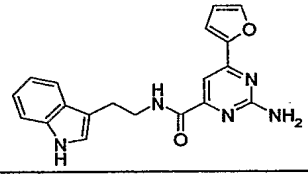
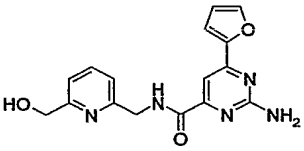
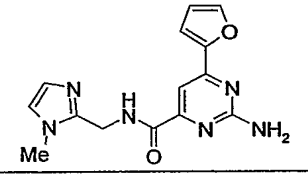
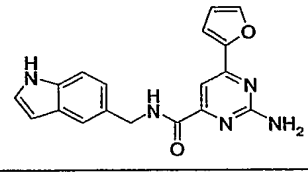
The invention is illustrated with reference to the following Examples, as set out in Table 1.

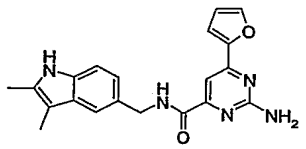
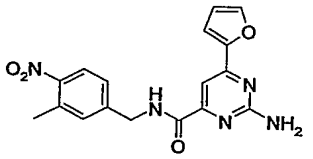
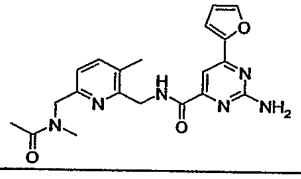
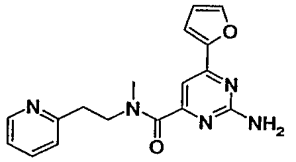
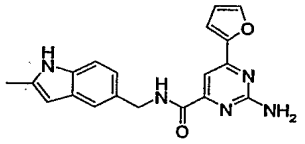
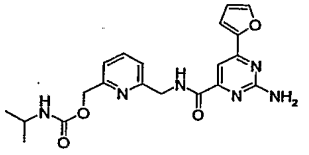
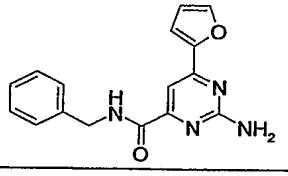
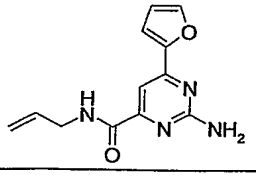
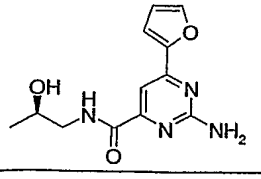
Table 1

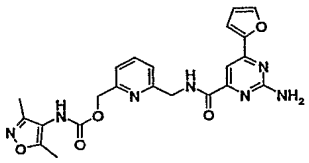
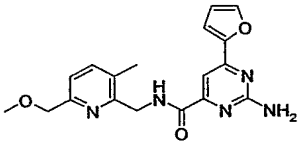
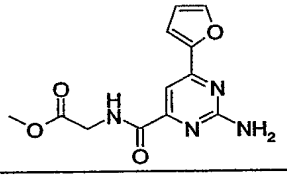
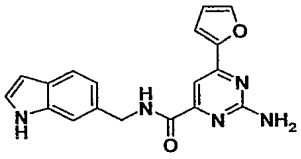
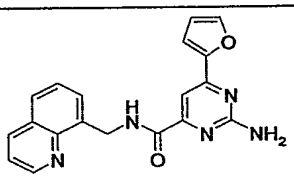
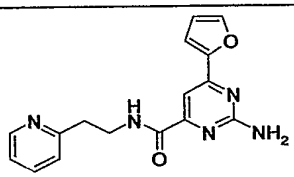
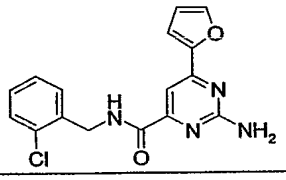
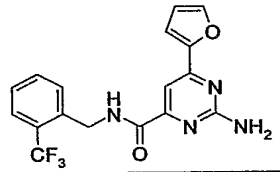
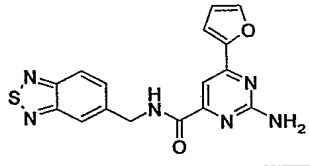
Example	Structure	Compound Name
1		2-Amino-*N*-(2-fluorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
2		2-Amino-*N*-(3,4-difluorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
3		2-Amino-6-(2-furyl)-*N*-(3-methoxybenzyl)pyrimidine-4-carboxamide
4		2-Amino-6-(2-furyl)-*N*,*N*-dimethylpyrimidine-4-carboxamide
5		1-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)piperidine
6		2-Amino-6-(2-furyl)-*N*-(2-methoxybenzyl)pyrimidine-4-carboxamide
7		2-Amino-6-(2-furyl)-*N*-(2-furylmethyl)pyrimidine-4-carboxamide
8		2-Amino-6-(2-furyl)pyrimidine-4-carboxamide

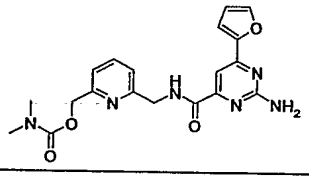
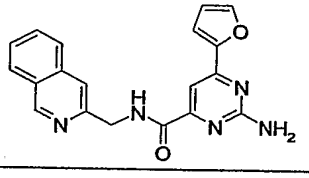
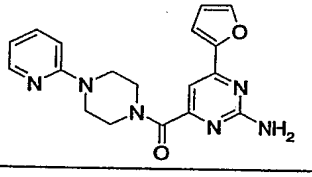
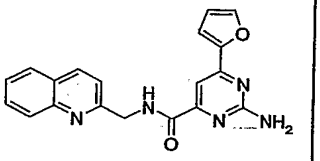
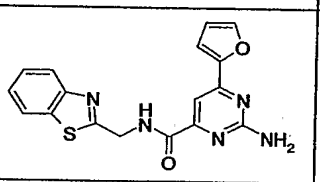
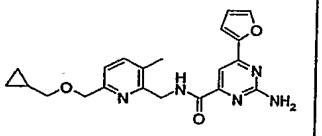
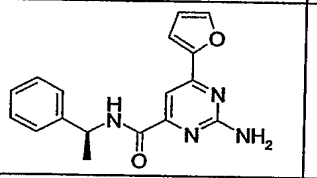
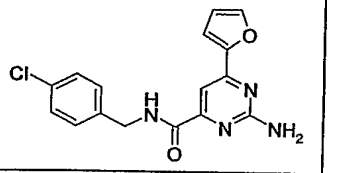
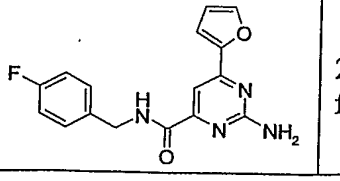
9		2-Amino-6-(2-furyl)-*N*-(4-dimethylaminobenzyl)pyrimidine-4-carboxamide
10		2-Amino-6-(2-furyl)-*N*-(6-methoxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
11		2-Amino-6-(2-furyl)-*N*-(3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
12		2-Amino-6-(2-furyl)-*N*-(3-(dimethylaminocarbonyl)benzyl)pyrimidine-4-carboxamide
13		2-Amino-6-(2-furyl)-*N*-(2-pyridylmethyl)pyrimidine-4-carboxamide
14		2-Amino-6-(2-furyl)-*N*-(4-pyridylmethyl)pyrimidine-4-carboxamide
15		2-Amino-6-(2-furyl)-*N*-(2-methylbenzyl)pyrimidine-4-carboxamide
16		2-Amino-*N*-(3-trifluoromethylbenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
17		2-Amino-*N*-(benzimidazol-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide

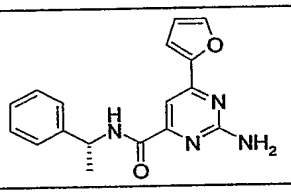
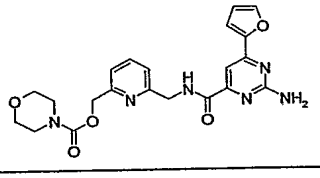
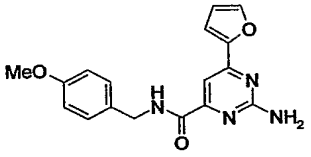
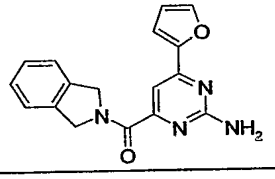
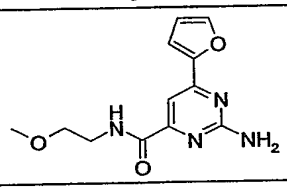
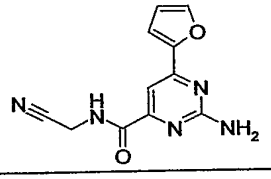
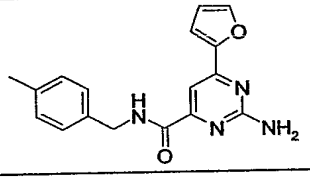
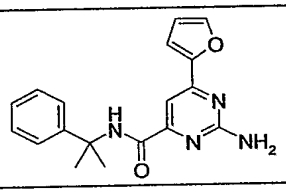
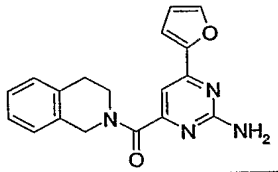
18		2-Amino-6-(2-furyl)-*N*-(3-pyridylmethyl)pyrimidine-4-carboxamide
19		2-Amino-6-(2-furyl)-*N*-(3-methylbenzyl)pyrimidine-4-carboxamide
20		2-Amino-6-(2-furyl)-*N*-(3-methoxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
21		2-Amino-6-(2-furyl)-*N*-(3-dimethylaminomethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
22		2-Amino-6-(2-furyl)-*N*-(3-(4-morpholinylmethyl)pyridin-2-ylmethyl)pyrimidine-4-carboxamide
23		2-Amino-6-(2-furyl)-*N*-(3,6-dimethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
24		2-Amino-6-(2-furyl)-*N*-(2-(2-thienyl)thiazol-4-ylmethyl)pyrimidine-4-carboxamide
25		2-Amino-6-(2-furyl)-*N*-(2-thienylmethyl)pyrimidine-4-carboxamide
26		2-Amino-6-(2-furyl)-*N*-(5-(2-pyridyl)-2-thienylmethyl)pyrimidine-4-carboxamide

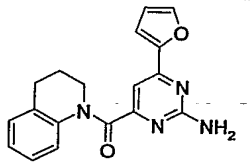
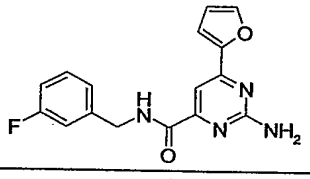
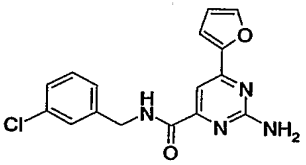
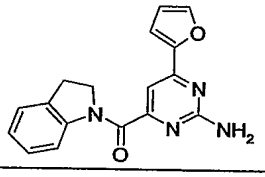
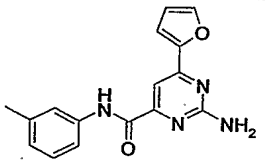
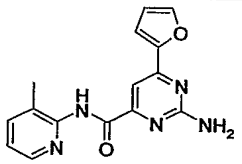
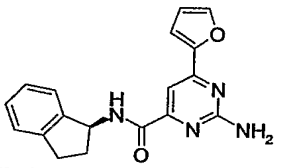
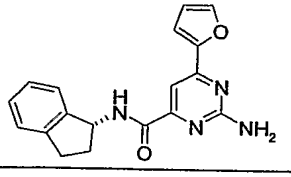
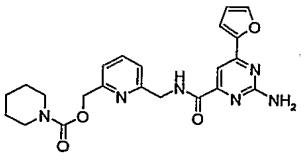
27		2-Amino-6-(2-furyl)-*N*-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)pyrimidine-4-carboxamide
28		2-Amino-6-(2-furyl)-*N*-(5-methylisoxazol-3-ylmethyl)pyrimidine-4-carboxamide
29		2-Amino-6-(2-furyl)-*N*-[3-(2-methoxy-6-methylpyridin-3-ylmethyl)pyrimidine-4-carboxamide
30		2-Amino-6-(2-furyl)-*N*-(6-fluoro[1,3]benzodioxin-8-ylmethyl)pyrimidine-4-carboxamide
31		2-Amino-6-(2-furyl)-*N*-6-methylpyridin-3-ylmethyl)pyrimidine-4-carboxamide
32		2-Amino-6-(2-furyl)-*N*-(3-indolylmethyl)pyrimidine-4-carboxamide
33		2-Amino-6-(2-furyl)-*N*-(6-hydroxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
34		2-Amino-6-(2-furyl)-*N*-(1*H*-1-methylimidazol-2-ylmethyl)pyrimidine-4-carboxamide
35		2-Amino-6-(2-furyl)-*N*-(5-indolylmethyl)pyrimidine-4-carboxamide

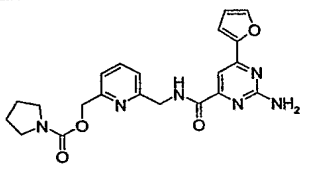
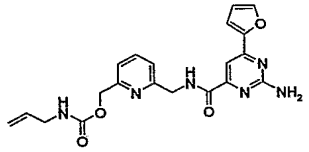
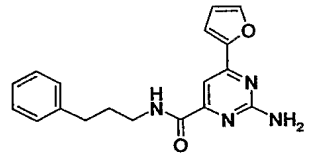
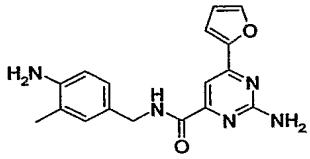
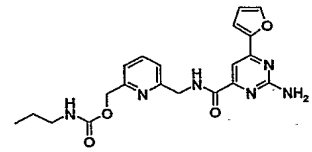
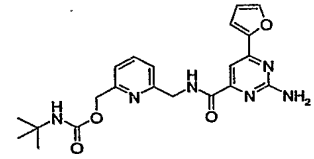
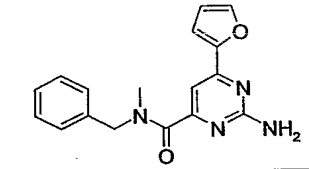
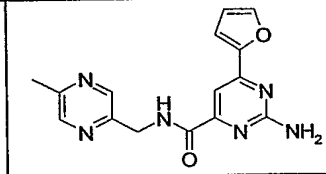
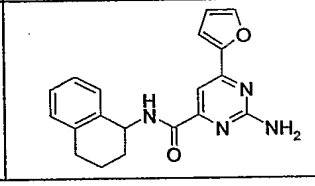
36		2-Amino-*N*-(2,3-dimethylindol-5-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
37		2-Amino-6-(2-furyl)-*N*-(3-methyl-4-nitrobenzyl)pyrimidine-4-carboxamide
38		*N*-(6-(N-Acetyl-N-methylaminomethyl)-3-methylpyridin-2-ylmethyl)-2-amino-6-(2-furyl)pyrimidine-4-carboxamide
39		2-Amino-6-(2-furyl)-*N*-methyl-*N*-(2-(2-pyridyl)ethyl)pyrimidine-4-carboxamide
40		2-Amino-6-(2-furyl)-*N*-(2-methylindol-5-ylmethyl)pyrimidine-4-carboxamide
41		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl isopropylcarbamate
42		2-Amino-*N*-benzyl-6-(2-furyl)pyrimidine-4-carboxamide
43		*N*-Allyl-2-amino-6-(2-furyl)pyrimidine-4-carboxamide
44		(R)-2-Amino-6-(2-furyl)-*N*-(2-hydroxypropyl)pyrimidine-4-carboxamide

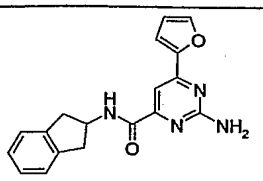
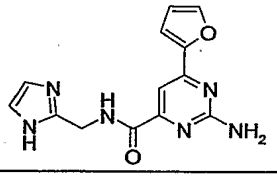
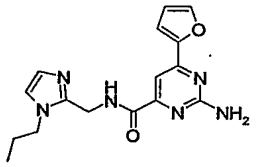
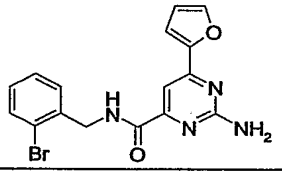
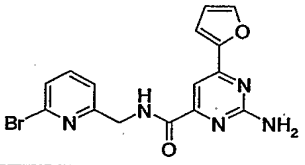
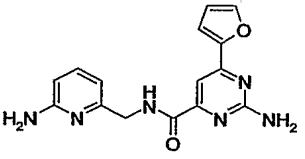
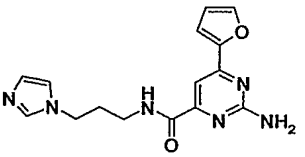
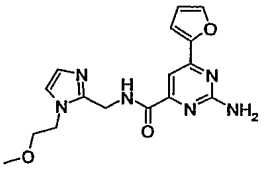
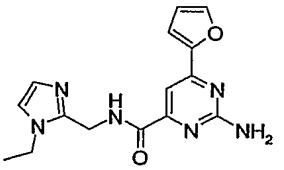
45		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl 3,5-dimethyloxazol-4-ylcarbamate
46		2-Amino-6-(2-furyl)-*N*-(6-methoxymethyl-3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
47		Methyl 6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidoacetate
48		2-Amino-6-(2-furyl)-*N*-(6-indolylmethyl)pyrimidine-4-carboxamide
49		2-Amino-6-(2-furyl)-*N*-(quinolin-8-ylmethyl)pyrimidine-4-carboxamide
50		2-Amino-6-(2-furyl)-*N*-(2-(pyridin-2-yl)ethyl)pyrimidine-4-carboxamide
51		2-Amino-*N*-(2-chlorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
52		2-Amino-6-(2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
53		2-Amino-*N*-([2,1,3]benzothiadiazol-5-ylmethyl) -6-(2-furyl)pyrimidine-4-carboxamide

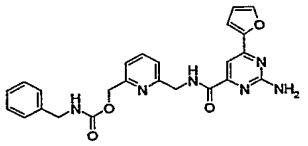
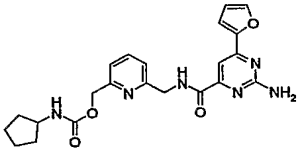
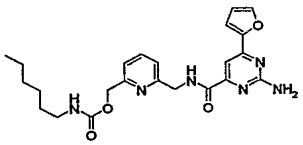
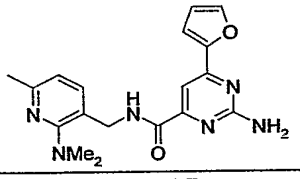
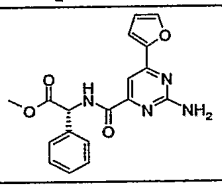
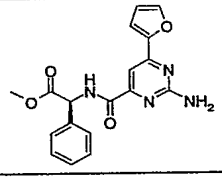
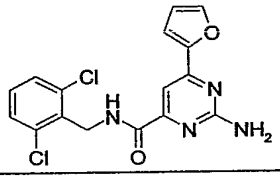
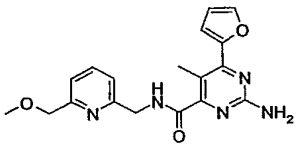
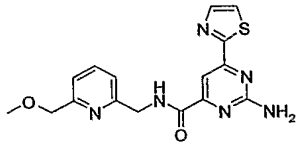
54		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl dimethylcarbamate
55		2-Amino-6-(2-furyl)-*N*-(isoquinolin-3-ylmethyl)pyrimidine-4-carboxamide
56		1-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-4-(2-pyridyl)piperazine
57		2-Amino-6-(2-furyl)-*N*-(quinolin-2-ylmethyl)pyrimidine-4-carboxamide
58		2-Amino-*N*-(benzothiazol-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
59		2-Amino-*N*-(6-cyclopropylmethoxymethyl-3-methylpyridin-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
60		(S)-2-Amino-6-(2-furyl)-*N*-(□-methylbenzyl)pyrimidine-4-carboxamide
61		2-Amino-*N*-(4-chlorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
62		2-Amino-*N*-(4-fluorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide

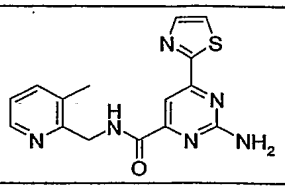
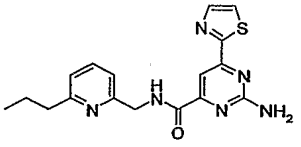
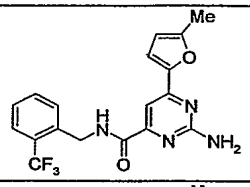
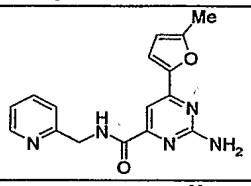
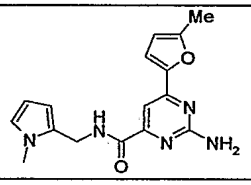
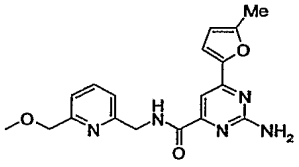
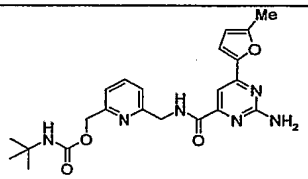
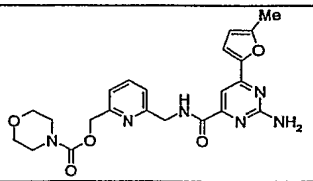
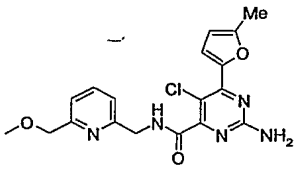
63		(R)-2-Amino-6-(2-furyl)-*N*-(□-methylbenzyl)pyrimidine-4-carboxamide
64		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl morpholine-1-carboxylate
65		2-Amino-6-(2-furyl)-*N*-(4-methoxybenzyl)pyrimidine-4-carboxamide
66		2-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-2,3-dihydro-1*H*-isoindole
67		2-Amino-6-(2-furyl)-*N*-(2-methoxyethyl)pyrimidine-4-carboxamide
68		2-Amino-*N*-(cyanomethyl)-6-(2-furyl)pyrimidine-4-carboxamide
69		2-Amino-6-(2-furyl)-*N*-(4-methylbenzyl)pyrimidine-4-carboxamide
70		2-Amino-*N*-(□,□-dimethylbenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
71		2-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-1,2,3,4-tetrahydroisoquinoline

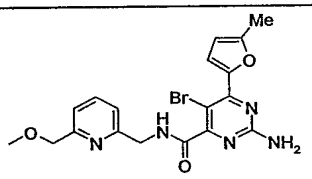
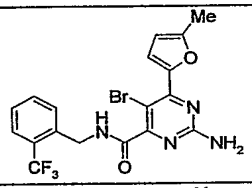
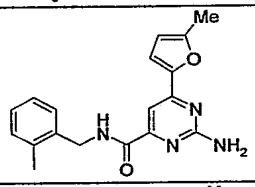
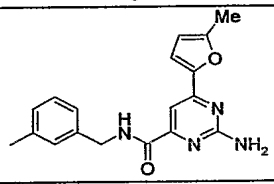
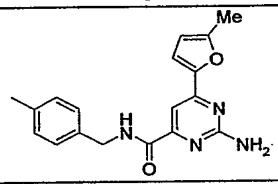
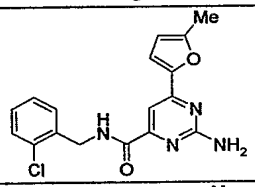
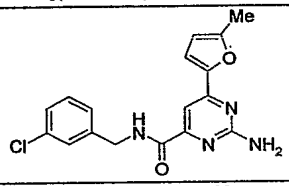
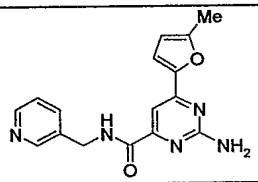
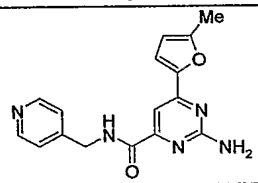
72		1-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-1,2,3,4-tetrahydroquinoline
73		2-Amino-*N*-(3-fluorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
74		2-Amino-*N*-(3-chlorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
75		1-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-2,3-dyhydroindole
76		2-Amino-6-(2-furyl)-*N*-(3-methylphenyl)pyrimidine-4-carboxamide
77		2-Amino-6-(2-furyl)-*N*-(3-methylpyridin-2-yl)pyrimidine-4-carboxamide
78		(R)-2-Amino-6-(2-furyl)-*N*-(1-indanyl)pyrimidine-4-carboxamide
79		(S)-2-Amino-6-(2-furyl)-*N*-(1-indanyl)pyrimidine-4-carboxamide
80		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl piperidine-1-carboxylate

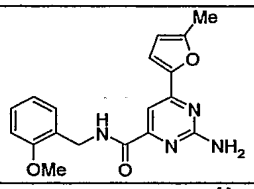
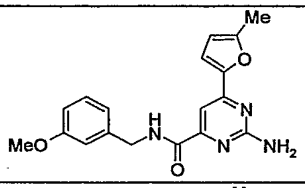
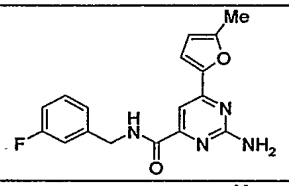
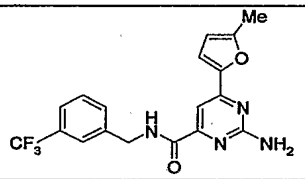
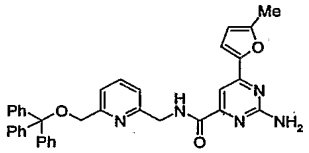
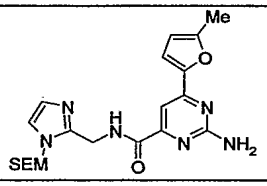
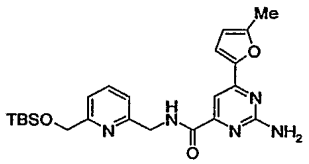
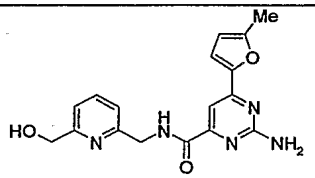
81		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl pyrrolidine-1-carboxylate
82		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl allylcarbamate
83		2-Amino-6-(2-furyl)-*N*-(3-phenylpropyl)pyrimidine-4-carboxamide
84		2-Amino-*N*-(4-amino-3-methylbenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
85		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl *n*-propylcarbamate
86		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl *tert*-butylcarbamate
87		2-Amino-N-benzyl-6-(2-furyl)-*N*-methylpyrimidine-4-carboxamide
88		2-Amino-6-(2-furyl)-*N*-(5-methylpyrazin-2-ylmethyl)pyrimidine-4-carboxamide
89		(R,S)-2-Amino-6-(2-furyl)-*N*-(1,2,3,4-tetrahydro-1-naphthyl)pyrimidine-4-carboxamide

90		2-Amino-6-(2-furyl)-*N*-(2-indanyl)pyrimidine-4-carboxamide
91		2-Amino-6-(2-furyl)-*N*-(1*H*-imidazol-2-ylmethyl)pyrimidine-4-carboxamide
92		2-Amino-6-(2-furyl)-*N*-(1-*n*-propylimidazol-2-ylmethyl)pyrimidine-4-carboxamide
93		2-Amino-*N*-(2-bromobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
94		2-Amino-*N*-(6-bromo-2-pyridylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
95		2-Amino-*N*-(6-amino-2-pyridylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
96		2-Amino-6-(2-furyl)-*N*-(3-(imidazol-1-yl)propyl)pyrimidine-4-carboxamide
97		2-Amino-6-(2-furyl)-*N*-(1-methoxymethylimidazol-2-ylmethyl)pyrimidine-4-carboxamide
98		2-Amino-*N*-(1-ethylimidazol-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide

99		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl benzylcarbamate
100		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl cyclopentylcarbamate
101		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl *n*-hexylcarbamate
102		2-Amino-*N*-(2-dimethylamino-6-methylpyridin-3-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
103		(R)-Methyl 2-(6-(2-amino-6-(2-furyl)pyrimidine-4-carboxamido))phenylacetate
104		(S)-Methyl 2-(6-(2-amino-6-(2-furyl)pyrimidine-4-carboxamido))phenylacetate
105		2-Amino-*N*-(2,6-dichlorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
106		2-Amino-6-(2-furyl)-*N*-(6-methoxymethyl-2-pyridylmethyl)-5-methylpyrimidine-4-carboxamide
107		2-Amino-*N*-(6-methoxymethyl-2-pyridylmethyl)-6-(thiazol-2-yl)pyrimidine-4-carboxamide

108		2-Amino-*N*-(3-methyl-2-pyridylmethyl)-6-(thiazol-2-yl)pyrimidine-4-carboxamide
109		2-Amino-*N*-(6-*n*-propyl-2-pyridylmethyl)-6-(thiazol-2-yl)pyrimidine-4-carboxamide
110		2-Amino-6-(5-methyl-2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
111		2-Amino-6-(5-methyl-2-furyl)-*N*-(2-pyridylmethyl)pyrimidine-4-carboxamide
112		2-Amino-6-(5-methyl-2-furyl)-*N*-(1-methyl-2-pyrrolylmethyl)pyrimidine-4-carboxamide
113		2-Amino-6-(5-methyl-2-furyl)-*N*-(6-methoxymethyl-2-pyridylmethyl)pyrimidine-4-carboxamide
114		6-(2-Amino-6-(5-methyl-2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl *tert*-butylcarbamate
115		6-(2-Amino-6-(5-methyl-2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl morpholine-1-carboxylate
116		2-Amino-5-chloro-*N*-(6-methoxymethyl-2-pyridylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide

117		2-Amino-5-bromo-*N*-(6-methoxymethyl-2-pyridylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
118		2-Amino-5-bromo-6-(5-methyl-2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
119		2-Amino-*N*-(2-methylbenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
120		2-Amino-*N*-(3-methylbenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
121		2-Amino-*N*-(4-methylbenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
122		2-Amino-*N*-(2-chlorobenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
123		2-Amino-*N*-(3-chlorobenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
124		2-Amino-6-(5-methyl-2-furyl)-*N*-(3-pyridylmethyl)pyrimidine-4-carboxamide
125		2-Amino-6-(5-methyl-2-furyl)-*N*-(4-pyridylmethyl)pyrimidine-4-carboxamide

126		2-Amino-*N*-(2-methoxybenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
127		2-Amino-*N*-(3-methoxybenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
128		2-Amino-*N*-(3-fluorobenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
129		2-Amino-6-(5-methyl-2-furyl)-*N*-(3-trifluoromethylbenzyl)pyrimidine-4-carboxamide
130		2-Amino-6-(2-furyl)-*N*-(6-(triphenylmethoxymethyl)pyridin-2-ylmethyl)pyrimidine-4-carboxamide
131		2-Amino-6-(2-furyl)-*N*-(1-(2-(trimethylsilyl)ethoxy)methyl-1*H*-imidazole-2-ylmethyl)pyrimidine-4-carboxamide
132		2-Amino-6-(5-methyl-2-furyl)-*N*-(6-(*tert*-butyldimethylsilyloxymethyl)pyridin-2-ylmethyl)pyrimidine-4-carboxamide
133		2-Amino-6-(5-methyl-2-furyl)-*N*-(6-hydroxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide

The general synthetic methods used for the preparation of these Examples are set out below as Methods A to AF. Table 2 sets out the Method used and yield obtained for each Example, together with the analytical data.

Method A

2-Amino-4-chloro-6-(2-furyl)pyrimidine

A solution of 2-(tributylstannyl)furan (35.7 g, 100 mmol) in DMF (100 mL) was treated with 2-amino-4,6-dichloropyrimidine (16.4 g, 100 mmol) and dichlorobis(triphenylphosphine)palladium (II) (3.51 g, 5.0 mmol). The suspension was stirred at 80 °C for 18 h, allowed to cool to room temperature and poured onto ice (400 g). The solid precipitate was filtered off, washed with water, dried in air, and the filtrate was extracted with EtOAc (300 mL), washed with water (100 mL), mixed with the solid precipitate and concentrated. The crude product was purified by chromatography [SiO_2; EtOAc:toluene (0:1 – 1:9 – 2:3)] and the material with R_f 0.23 (isopropyl ether) was triturated with isohexane to give the *title compound* (11.1 g, 57 %) as a yellow solid; m.p. 133-140 °C; NMR δ_H (400 MHz, DMSO) 6.70 (1H, q, *J* 2.0 Hz), 6.95 (1H, s), 7.16 (2H, br s), 7.27 (1H, d, *J* 3.6 Hz), 7.92 (1H, t, *J* 1.0 Hz).

Method B

2-Amino-6-(2-furyl)pyrimidine-4-carbonitrile

A solution of 2-amino-4-chloro-6-(2-furyl)pyrimidine (9.78 g, 50.0 mmol) in DMSO (200 mL) was treated with sodium cyanide (14.7 g, 300 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.56 g, 5.0 mmol). The suspension was stirred for 4 days, and more DABCO (5.04 g, 45 mmol) and DMSO (100 mL) were added. The suspension was stirred for a further 2 days, poured onto a mixture of ice (750 g) and water (750 mL), the crude product was filtered off, washed with water and MeCN, and dried in air to give the *title compound* (7.1 g, 77 %) as a brown solid; m.p. 193 - 194 °C; NMR δ_H (400 MHz, DMSO) 6.74 (1H, q, *J* 1.6 Hz), 7.32 (2H, br s), 7.39 (1H, d, *J* 3.6 Hz), 7.43 (1H, s), 7.98 (1H, d, *J* 1.2 Hz); M/Z 187 $(M+H)^+$.

The following novel nitriles were synthesised from the appropriate 4-chloropyrimidine by Method B.

2-Amino-6-(5-methyl-2-furyl)pyrimidine-4-carbonitrile

NMR δ_H (400 MHz, DMSO) 2.38 (3H, s), 6.37 – 6.38 (1H, m), 7.28 (2H, s), 7.32 (1H, d, *J* 3.5 Hz), 7.37 (1H, s); M/Z 201 $(M+H)^+$

2-Amino-6-(2-thiazolyl)pyrimidine-4-carbonitrile

2-Amino-6-(4-methylthiazol-2-yl)pyrimidine-4-carbonitrile

Method C

2-Amino-6-(2-furyl)pyrimidine-4-carboxylic acid

A suspension of 2-amino-6-(2-furyl)pyrimidine-4-carbonitrile (7.06 g, 37.9 mmol) in water (30 mL) was treated carefully with concentrated sulfuric acid (30 mL), stirred at 100 °C for 2 h, allowed to cool to room temperature and poured onto a mixture of ice (150 g) and water (150 mL). After standing for 1 h the crude product was filtered off, washed with water and MeCN, and dried in air to give the *title compound* (7.02 g, 90 %) as a brown solid; NMR δ_H (400 MHz, DMSO) 6.71 (1H, dd, *J* 1.6, 3.6 Hz), 7.04 (2H, br s), 7.30 (1H, d, *J* 3.6 Hz), 7.36 (1H, s), 7.94 (1H, d, *J* 1.2 Hz).

The following novel carboxylic acids were synthesised from the appropriate pyrimidine-4-carbonitrile by Method C.

2-Amino-6-(5-methyl-2-furyl)pyrimidine-4-carboxylic acid

NMR δ_H (400 MHz, DMSO) 2.38 (3H, s), 6.33 – 6.34 (1H, m), 6.97 (2H, s), 7.21 (1H, d, *J* 3.0 Hz), 7.30 (1H, s), 13.12 (1H, s); M/Z 220 $(M+H)^+$

2-Amino-6-(2-thiazolyl)pyrimidine-4-carboxylic acid

2-Amino-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxylic acid

Method D

2-Amino-6-(2-furyl)-*N*-(3-methylpyridin-2-yl)methylpyrimidine-4-carboxamide (Example 11)

A suspension of 2-amino-6-(2-furyl)pyrimidine-4-carboxylic acid (206 mg, 1.0 mmol) in DMF (5 mL) was treated with N,N'-carbonyldiimidazole (162 mg, 1.0 mmol), stirred for 2 h, treated with 3-methylpyridine-2-methanamine (244 mg, 2.0 mmol), stirred for 2 h, poured onto water (50 mL) and extracted with EtOAc (2 x 25 mL). The extracts were washed with water, concentrated *in vacuo*, and the crude product was triturated with ether to give the *title compound* (109 mg, 35 %) as a yellow solid.

Method E

2-[(6-Methoxymethyl)pyridin-2-yl]methylisoindole-1,3(2*H*)-dione

A solution of 2-[(6-hydroxymethyl)pyridin-2-yl]methylisoindole-1,3(2*H*)-dione (4.02 g, 15.0 mmol) in DMF (20 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil, 600 mg, 15.0 mmol), stirred for 15 min at 0 °C, treated with methyl iodide (1.03 ml, 16.5 mmol), warmed to room temperature and stirred for 2 days. The reaction mixture was poured onto water (100 mL), extracted with EtOAc (3 x 100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography [SiO_2; isohexane:EtOAc (1:4)] to give the *title compound* (1.11 g, 26 %) as a white solid; NMR δ_H (400 MHz, $CDCl_3$) 3.42 (3H, s), 4.51 (2H, s), 5.01 (2H, s), 7.10 (1H, d, *J* 8.0 Hz), 7.30 (1H, d, *J* 8.0 Hz), 7.63 (1H, t, *J* 7.5 Hz), 7.73 – 7.76 (2H, m), 7.87 – 7.91 (2H, m); R_f (EtOAc) = 0.77.

Method F

6-Methoxymethylpyridine-2-methanamine

A solution of 2-[(6-methoxymethyl)pyridin-2-yl]methylisoindole-1,3(2*H*)-dione (1.11 g, 3.94 mmol) in EtOH (75 mL) was treated with hydrazine hydrate (0.95 mL, 19.5 mmol), stirred at 80 °C overnight, cooled to room temperature, filtered through Celite and concentrated *in vacuo* to give the *title compound* (265 mg, 44 %) as a yellow oil; NMR δ_H (400 MHz, $CDCl_3$) 2.10 (2H, br s), 3.48 (3H, s), 3.97 (2H, s), 4.57 (2H, s), 7.18 (1H, d, *J* 8.0 Hz), 7.28 (1H, d, *J* 8.0 Hz), 7.66 (1H, t, *J* 7.5 Hz).

Method G

3-Methoxymethylpyridine-2-carbonitrile

A stirred solution of 3-bromomethylpyridine-2-carbonitrile (591 mg, 3.0 mmol) in MeOH (10 mL) at 0 °C was treated with NaOMe (324 mg, 6.0 mmol), warmed to room temperature, stirred for 2 h, concentrated *in vacuo* and partitioned between EtOAc (50 mL) and water (30 mL). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography [SiO_2; hexane:EtOAc (9:1 - 4:1)] to give the *title compound* (297 mg, 67 %) as a clear oil; NMR δ_H (400 MHz, $CDCl_3$) 3.51 (3H, s), 4.68 (2H, s), 7.50 – 7.55 (1H, m), 7.92 – 7.96 (1H, m), 8.63 (1H, dd, *J* 5.0, 1.5 Hz); R_f [isohexane:EtOAc (4:1)] = 0.65.

The following novel nitriles were synthesised from 6-bromomethyl-3-methylpyridine-2-carbonitrile by Method G.

6-Methoxymethyl-3-methylpyridine-2-carbonitrile

NMR δ_H (400 MHz, $CDCl_3$) 2.55 (3H, s), 3.47 (3H, s), 4.56 (2H, s), 7.56 (1H, d, *J* 8.0 Hz), 7.67 (1H, d, *J* 8.5 Hz); LC 1.6 min. (20/50).

6-Cyclopropylmethoxymethyl-3-methylpyridine-2-carbonitrile

NMR δ_H (400 MHz, $CDCl_3$) 0.24 – 0.28 (2H, m), 0.56 – 0.61 (2H, m), 1.09 – 1.18 (1H, m), 2.57 (3H, s), 3.42 (2H, d, *J* 7.0 Hz), 4.66 (2H, s), 7.63 (1H, d, *J* 8.0 Hz), 7.68 (1H, d, *J* 8.0 Hz); LC 1.2 min. (50/80).

Method H

3-(*N*,*N*-Dimethylamino)methylpyridine-2-carbonitrile

A solution of 3-bromomethylpyridine-2-carbonitrile (591 mg, 3.0 mmol) in MeCN (10 mL) was treated with dimethylamine (7.9-M in water, 1.9 mL, 15 mmol) and heated at 50 °C for 4 h. The solution was treated with MP-carbonate (2.0 g, 6.0 mmol), stirred for 30 min, filtered through Celite and the residue was washed with EtOAc. The filtrate was concentrated *in vacuo*, and the crude product was purified by chromatography [SiO_2; MeOH:EtOAc:isohexane (0:4:1 - 1:9:0)] to give the *title compound* (541 mg, 96 %) as an orange oil; NMR δ_H (400 MHz, $CDCl_3$) 2.31 (6H, s), 3.67 (2H, s), 7.50 (1H, dd, *J* 8.0, 4.5 Hz), 7.94 (1H, dd, *J* 8.0, 1.5 Hz), 8.61 (1H, dd, *J* 4.5, 1.5 Hz); M/Z 162 $(M+H)^+$.

The following novel compound was synthesised from 3-bromomethylpyridine-2-carbonitrile and morpholine by Method H.

3-(4-Morpholinyl)methylpyridine-2-carbonitrile

NMR δ_H (400 MHz, $CDCl_3$) 2.50 – 2.55 (4H, m), 3.68 – 3.74 (6H, m), 7.50 (1H, dd, *J* 8.0, 5.0 Hz), 7.92 – 7.95 (1H, m), 8.62 (1H, dd, *J* 4.5, 1.5 Hz); M/Z 204 $(M+H)^+$.

Method I

3,6-Dimethylpyridine-2-methanamine

A solution of 3,6-dimethylpyridine-2-carbonitrile (264 mg, 2.00 mmol) in EtOH (10 mL) was treated with Raney-Ni (approximately 100 mg) and stirred under an atmosphere of hydrogen for 4 h at room temperature. The mixture was filtered through Celite and concentrated *in vacuo* to give the *title compound* (270 mg, 99 %) as a yellow oil; NMR δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s), 2.51 (3H, s), 4.17 (2H, s), 7.00 (1H, d, *J* 7.5 Hz), 7.37 (1H, d, *J* 7.5 Hz); M/Z 137$(M+H)^+$.

The following novel amines were also synthesised by Method I from the appropriate nitrile.

3-Methoxymethylpyridine-2-methanamine

M/Z 153 $(M+H)^+$.

3-(*N*,*N*-Dimethylamino)methylpyridine-2-methanamine

M/Z 166 $(M+H)^+$.

3-(4-Morpholinyl)methylpyridine-2-methanamine

NMR δ_H (400 MHz, $CDCl_3$) 2.41 – 2.47 (4H, m), 3.50 (2H, s), 3.68 (4H, t, *J* 4.5 Hz), 4.02 (2H, s), 7.14 (1H, dd, *J* 7.5, 4.5 Hz), 7.54 (1H, dd, *J* 7.5, 1.5 Hz), 8.49 (1H, dd, *J* 5.0, 1.5 Hz); M/Z 208 $(M+H)^+$.

2-Dimethylamino-6-methylpyridine-3-methanamine

NMR δ_H (400 MHz, $CDCl_3$) 1.79 (2H, s), 2.45 (3H, s), 2.85 (6H, s), 3.96 (2H, s), 6.74 (1H, d, *J* 7.5 Hz), 7.46 (1H, d, *J* 7.5 Hz).

6-Methoxymethyl-3-methylpyridine-2-methanamine

NMR δ_H (400 MHz, $CDCl_3$) 1.74 (2H, s), 2.28 (3H, s), 3.47 (3H, s), 3.94 (2H, s), 4.55 (2H, s), 7.18 – 7.20 (1H, m), 7.41 – 7.44 (1H, m); M/Z 167 $(M+H)^+$

6-Cyclopropylmethoxymethyl-3-methylpyridine-2-methanamine

NMR δ_H (400 MHz, $CDCl_3$) 0.22 – 0.28 (2H, m), 0.54 – 0.61 (2H, m), 1.08 – 1.19 (1H, m), 1.76 (2H, s), 2.30 (3H, s), 3.41 – 3.43 (2H, m), 3.96 (2H, s), 4.65 (2H, d, *J* 4.0 Hz), 7.25 – 7.27 (1H, m), 7.42 – 7.45 (1H, m); LC 0.73 min. (20/50).

3-Aminomethyl-N,N-dimethylbenzamide

NMR δ_H (400 MHz, DMSO) 1.92 – 3.54 (2H, s), 2.94 (6H, d, *J* 26.0 Hz), 3.71 (2H, s), 7.05 – 7.48 (4H, m)

1-(2-(Trimethylsilyl)ethoxy)methyl-1H-imidazole-2-methanamine dihydrochloride

NMR δ_H (400 MHz, DMSO) 0.00 (9H, s), 0.93-0.89 (2H, m), 3.55-3.59 (2H, m), 4.40 (2H, s), 5.64 (2H, s), 7.57 (1H, s), 7.75 (1H, s), 8.94 (2H, br s); M/Z 228 $(M+H)^+$

N-(6-Aminomethyl-5-methylpyridine-2-ylmethyl)-N-methylacetamide

NMR 1:1 rotamers 7.42 (0.5H, d, *J* 7.5), 7.37 (0.5H, d, *J* 7.5), 7.03 (0.5H, d, *J* 7.5), 6.93 (0.5H, d, *J* 7.5), 4.67 (1H, s), 4.58 (1H, s), 3.94 (1H, s), 3.92 (1H, s), 3.07 (1.5H, s), 2.98 (1.5H, s), 2.27 (1.5H, s), 2.25 (1.5H, s), 2.17 (1.5H, s), 2.16 (1.5H, s); M/Z 208 $(M+H)^+$

Method J

2-Amino-6-(2-furyl)-*N*-(5-indolylmethyl)pyrimidine-4-carboxamide (Example 35)

A mixture consisting of 2-amino-6-(2-furyl)pyrimidine-4-carboxylic acid (206 mg, 1.0 mmol), the indole-5-methanamine (146 mg, 1.0 mmol), polymer supported carbodiimide (Argonaut Technologies, loading 1.38 mmol/g, 1.10g, 1.5 mmol) and 1-hydroxybenzotriazole hydrate (203 mg, 1.5 mmol) in DMF (5 mL) was stirred at room temperature for 24 hr. The mixture was filtered through a pad of Celite, washing through

with EtOAc. The filtrate was washed successively with H_2O (10 mL), 2-M Na_2CO_3 (2 x 10 mL) and H_2O (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was dissolved in MeOH (1.0 mL), added dropwise with stirring to H_2O (2 mL) and the resulting precipitate filtered to give the *title compound* (198 mg, 59 %) as a cream solid.

Method K

2-Amino-*N*-benzyl-6-(2-furyl)pyrimidine-4-carboxamide (Example 42)

A solution of 2-amino-6-(2-furyl)pyrimidine-4-carboxylic acid (103 mg, 0.5 mmol) in DMF (2 mL) was treated with benzylamine (59 mg, 0.55 mmol), EDCI (104 mg, 0.54 mmol) and 4-dimethylaminopyridine (66 mg, 0.54 mmol), stirred at room temperature for 17 h, poured into water (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic phase was washed with water (25 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography (SiO_2; isopropyl ether:EtOAc, 100:0 – 0:100) to give the *title compound* (52 mg, 40 %) as an off-white solid.

Method L

2-Bromomethyl-6-(triphenylmethoxymethyl)pyridine

A solution of 6-(triphenylmethoxymethyl)pyridine-2-methanol (16.8 g, 44 mmol) in CH_2Cl_2 at 0°C was treated with triphenylphosphine (17.3 g, 66 mmol) and carbon tetrabromide (17.5 g, 52.8 mmol), stirred at 0 °C for 2.5 h then concentrated *in vacuo* to approximately a quarter of the original volume. The resulting solution was filtered through a pad of silica, washed with hexane:EtOAc (1:1) and the filtrate concentrated *in vacuo* to give the *title compound* (16.8 g, 86 %) as a cream solid; NMR δ_H (400 MHz, DMSO) 4.14 (2H, s), 4.61 (2H, s), 7.27 – 7.48 (16H, m), 7.68 (1H, d, *J* 7.5 Hz), 7.90 (1H, t, *J* 7.5 Hz); Rf (Hexane:EtOAc (2:1))= 0.84

The following novel bromides were also synthesised by Method L from the appropriate alcohol.

6-Bromomethyl-3-methylpyridine-2-carbonitrile

NMR δ_H (400 MHz, DMSO) 7.68 (1H, d, *J* 8.5), 7.58 (1H, d, *J* 8.5), 4.52 (2H, s), 2.57 (3H, s); M/Z 211 $(M+H)^+$ and 213 $(M+H)^+$

Method M

2-(Azidomethyl)-6-(triphenylmethoxymethyl)pyridine

A solution of 2-bromomethyl-6-(triphenylmethoxymethyl)pyridine (3.04 g, 6.84 mmol) in DMF (25 mL) was treated with sodium azide (650 mg, 10 mmol) and stirred at room temperature for 20 h. The reaction was poured into water (100 mL), extracted with EtOAc (2 x 50mL) and the combined organic phase was washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the product (2.75 g, 99 %) as a yellow oil; IR ν_{max} (Film)/cm^{-1} 3060, 2103, 1679, 1594, 1448, 1096 and 706; NMR δ_H (400 MHz, $CDCl_3$) 4.36 (2H, s), 4.39 (2H, s), 7.20 – 7.33 (10H, m), 7.49 – 7.52 (6H, m), 7.72 – 7.80 (2H, m)

Method N

6-(Triphenylmethoxymethyl)pyridine-2-methanamine

A solution of 2-(azidomethyl)-6-(triphenylmethoxymethyl)pyridine (2.78 g, 6.8 mmol) in THF (25 mL) was treated with triphenylphosphine (1.96 g, 7.5 mmol), stirred at room temperature for 3 h, treated with water (184 µl, 10.2 mmol), stirred at room temperature for a further 7 days and concentrated *in vacuo*. The resulting oil was purified by chromatography [SiO_2; EtOAc:MeOH:NH_3 (1:0:0) to (9:1:0.2)] to give the *title compound* (2.33 g, 90 %) as a yellow oil; NMR δ_H (400 MHz, $CDCl_3$) 1.74 (2H, s), 3.90 (2H, s), 4.34 (2H, s), 7.14 – 7.33 (10H, m), 7.50 – 7.52 (6H, m), 7.65 – 7.74 (2H, m); M/Z 381 $(M+H)^+$

Method O

2-Amino-6-(2-furyl)-*N*-(6-hydroxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide (Example 33)

A solution of 2-amino-6-(2-furyl)-*N*-(6-(triphenylmethoxymethyl)pyridin-2-ylmethyl)pyrimidine-4-carboxamide (3.408 g, 6 mmol) in MeOH (50 mL) was treated with 4-M HCl in dioxane (7.5 ml, 30 mmol), stirred at room temperature for 20 h and concentrated *in vacuo*. The residue was diluted with water (50 mL) basified with 5-M NaOH, extracted with EtOAc (2 x 25 mL) and the combined organic phase washed with brine (25 mL), dried ($MgSO_4$), concentrated *in vacuo* to give the *title compound* (1.19 g, 61 %) as a cream solid.

Method P

2-Amino-6-(2-furyl)-*N*-(1*H*-imidazol-2-ylmethyl)pyrimidine-4-carboxamide (Example 91)

Conc. HCl (4 ml) was added dropwise to a solution of X (340 mg, 0.82 mmol) in methanol (20 ml) at 0 °C. The mixture was then stirred at 80 °C for 1 h. After cooling to room temperature the solvent was removed and the residue was triturated with diethyl ether. The resulting solid was filtered off and washed with diethyl ether to give X (230 mg, 78%) as the dihydrochloride salt.

The dihydrochloride salt (230 mg, 0.64 mmol) was stirred with sat. aq. $NaHCO_3$ (5 ml) to give the free base (165 mg, 0.58 mmol) after filtration.

Method Q

2-Amino-6-(2-furyl)-*N*-(1*H*-1-methylimidazol-2-ylmethyl)pyrimidine-4-carboxamide (Example 34)

Sodium hydride (44 mg, 1.11 mmol) was added to a solution of X (300 mg, 1.06 mmol) in *N,N*-dimethlyformamide (15 ml) at room temperature. After 20 min methyl iodide (99 □l, 1.58 mmol) was added and the mixture was stirred at room temperature fro 16 h. The mixture was poured onto water and extracted with ethyl acetate (x 3). The combined organic portions were dried and concentrated. The residue was purified by column chromatography (EtOAc) to give X (180 mg, 57%) as a yellow solid.

Method R

6-Hydroxymethyl-3-methylpyridine-2-carbonitrile

A solution of X (4.44 g, 30.0 mmol) and conc. H_2SO_4 (2 drops) in acetic anhydride (30 ml) was stirred at 100 °C for 16 h. After cooling to room temperature the mixture was poured onto water and the solution was basified to pH 8 with sat. aq. $NaHCO_3$. The solution was extracted with ethyl acetate (x 3), the organic portions were dried and evaporated. The residue was taken up in methanol (100 ml) and water (40 ml). K_2CO_3 (8.8 g) was added and the mixture was stirred at room temperature for 1 h. The mixture was concentrated, partitioned between ethyl acetate and water, the organic portion was separated, dried and evaporated to give X (2.4 g, 51%) as a yellow oil.

NMR 7.67 (1H, d, J 8.5), 7.42 (1H, d, J 8.5), 4.78 (2H, s), 2.57 (3H, s); M+1 149

Method S

N-(6-Cyano-5-methylpyridine-2-ylmethyl)-N-methylacetamide

Sodium hydride (228 mg, 5.69 mmol) was added to a solution of *N*-methylacetamide (416 mg, 5.69 mmol) in tetrahydrofuran (15 ml) at room temperature. After 15 min 6-bromomethyl-3-methylpyridine-2-carbonitrile (1.0 g, 4.74 mmol) was added and the mixture was stirred for 16 h. The mixture was poured onto water and extracted with ethyl acetate (x 3). The combined organic portions were dried and the solvent was evaporated to give X (665 mg, 69%) as a yellow oil.

NMR 7.61 (1H, d, J 8.0), 7.43 (1H, d, J 8.0), 4.65 (2H, s), 3.09 (3H, s), 2.53 (3H, s), 2.15 (3H, s); M+1 204

Method T

6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl isopropylcarbamate (Example 41)

A solution of 2-amino-6-(2-furyl)-*N*-(6-hydroxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide (200 mg, 0.61 mmol) in DMF was treated with iso-propyl isocyanate (86 µl, 0.915 mmol) and triethylamine (one drop) and shaken at 90°C for 20 h. TLC showed the reaction to be incomplete. The reaction was again treated with iso-propyl isocyanate (57 µl, 0.61 mmol) and shaken at 90°C for a further 20 h. The reaction was concentrated *in vacuo* to dryness and purified by **prep LC**. The product was isolated by filtration to give the product (70 mg, 28%) as a beige solid.

Method U

6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl dimethylcarbamate (Example 54)

A stirred solution of 2-amino-6-(2-furyl)-*N*-(6-hydroxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide (50mg, 0.15 mmol) in DMF at 0°C was treated with sodium hydride (6 mg, 0.15 mmol). After 5 min the reaction was treated with dimethylcarbamyl chloride (14 µl, 0.15 mmol) and stirred at room temperature for 1 h. The reaction was diluted with water and the solid precipitate was isolated by filtration to give the product (35 mg, 58%) as a cream solid.

Method V

2-Amino-*N*-(4-amino-3-methylbenzyl)-6-(2-furyl)pyrimidine-4-carboxamide (Example 84)

A freshly prepared solution of $SnCl_2$ dihydrate (193 mg, 0.857 mmol) in concentrated HCl (0.7 mL) was added dropwise to a suspension of 2-amino-6-(2-furyl)-*N*-(3-methyl-4-nitrobenzyl)pyrimidine-4-carboxamide (101 mg, 0.29 mmol) in EtOH (3 mL) at 50 °C. The reaction temperature was increased to 70 °C and the mixture heated at this temperature for 24 hr. The yellow precipitate (crude HCl salt) was collected by filtration, washed with a little EtOH, slurried with 2.5 M NaOH solution and filtered again. The collected solid was taken up into hot THF, passed through a pad of silica, and the filtrate evaporated to leave yellow oil. This oil was taken up into MeOH, the solution treated with HCl (4M in dioxane, 0.5 mL), stirred for 24 hr and filtered to give the title compound (31 mg, 35 %) as a grey solid.

Method W

2-Amino-*N*-(6-amino-2-pyridylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide (Example 95)

A 4M solution of NH_4OH in ethylene glycol (20.23 ml, 80.92 mmol) is treated with 2-amino-*N*-(6-bromo-2-pyridylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide (350 mg, 0.93 mmol) and copper(I)oxide (6.7 mg, 0.046 mmol). The reaction mixture was contained within a sealed tube and stirred at 90°C for 20 h. The reaction was then poured into water (100ml) and extracted with EtOAc, washed with brine. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The solid was purified by column chromatography [SiO_2; Hexane:EtOAc (1:4) to (0:1)] to give the product (65 mg, 22%) as a cream solid.

Method X

2-Amino-6-(2-furyl)-5-methylpyrimidine-4-carbonitrile

A solution of 4-chloro-6-(2-furyl)-5-methylpyrimidine-2-ylamine (80 mg, 0.38 mmol) in acetonitrile (4 mL) was treated with polymer supported cyanide (0.636 mg, 1.91 mmol),

heated with stirring at 140 °C in the microwave for 30 min., filtered to remove the resin and the filter cake washed with acetonitrile. The filtrate was concentrated *in vacuo* to give the *title compound* (50 mg, 65 %) as off-white solid; NMR δ_H (400 MHz, DMSO) 8.0(1H, dd, J 0.7Hz, 1.7Hz), 7.28 (1H,dd, 0.7Hz, J 3.5Hz), 7.04 (2H br s), 6.75 (1H, dd, J 1.7Hz, J 3.5Hz) and 2.48 (3H, s); M/Z 201 (M=H)+; LC 1.1 min. (50/80).

Method Y

4-Hydroxy-6-(2-thiazolyl)pyrimidine-2-amine

Guanidine carbonate (3.48 g, 19.32 mmol) was suspended in EtOH (100 mL) and toluene (20 mL) and 50 mL of the solvent was distilled off using a Dean & Stark apparatus. The suspension was cooled to 40 °C, treated with a solution of ethyl β-oxo-2-thiazolepropionate (7.7 g, 38.65 mmol) in EtOH (20 mL), refluxed for 40 h, cooled, treated with water (50 mL) and refluxed for 30 min. The suspension was cooled to 0 °C, treated with a solution of conc. HCl (4 mL) in water (40 mL), stirred at 0 °C for 30 min and the resulting precipitate filtered, washed with water (2 x 25 mL) and MeCN (2 x 25 mL) and air dried to give the product (2.7 g, 36 %) as a yellow solid. Data available.

The following novel compound was also synthesised by Method Y from ethyl 4-methyl-β-oxo-2-thiazolepropionate.

4-Hydroxy-6-(4-methylthiazol-2-yl)pyrimidine-2-amine

NMR δ_H (400 MHz, DMSO) 2.42 (3H, s), 6.21 (1H, s), 6.75 (2H, br s), 7.45 (1H, s) and 10.90 (1H, br s); M/Z 209 $(M+H)^+$; Anal. Calc for $C_8H_8N_4OS$: C, 46.14; H, 3.87; N, 26.89. Found: C, 46.04; H, 3.91; N, 26.53.

Method Z

4-Chloro-6-(2-thiazolyl)pyrimidine-2-amine

A suspension of the 4-Hydroxy-6-(2-thiazolyl)pyrimidine-2-amine (2.64 g, 13.6 mmol) in $POCl_3$ (30 mL) was heated at 120 °C for 3 h, cooled and concentrated *in vacuo*. The resulting brown solid was added to ice/water (200 g), basified with NH_4OH (8 mL) and the

resulting solid was filtered and purified by chromatogtraphy (SiO_2, EtOAc : isohexane 2:3 – 1:0) to give the product (1.73 g, 60 %) as a pale yellow solid.

Method AA

Ethyl 4-methyl-β-oxo-2-thiazolepropionate

NaH (60% in oil, 1.34 g, 33.5 mmol) was washed with isohexane (2 x 14 mL), suspended in toluene (25 mL), treated with diethyl carbonate (4.7 mL, 4.6 g, 38.8 mmol), heated to 80 °C, treated dropwise over 20 min with a solution of 2-acetyl-4-methylthiazole (2.72 g, 19.2 mmol) in toluene (5 mL) and stirred at 80 °C for 2 h. The mixture was cooled to 0 °C, treated dropwise with HOAc (4.65 mL, 4.9 g, 81 mmol) followed by ice (25 g) and water (50 mL) and stirred for 30 min. The aqueous phase was extracted with toluene (50 mL), the combined organic phase was washed with water (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (3 g, 74 %) as a dark red oil, used in the next step without further purification; NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.2 Hz), 2.92 (3H, s), 4.14 (2H, s), 4.18 – 4.25 (2H, m) and 7.31 (1H, s).

Method AB

4-Chloro-6-(5-methyl-2-furyl)pyrimidine-2-amine

A solution of 2-methylfuran (11 ml, 122 mmol) and N, N, N', N'-tetramethylethylenediamine (18.4 ml, 122 mmol) in anhydrous THF (500 mL) at ⁻78 °C under nitrogen was treated with n-butyl lithium (48.8 ml, 122 mmol), stirred at ⁻78 °C for 20 min, warmed to 0 °C for 30 min and then warmed to room temperature for 15 min. The reaction was cooled to ⁻78 °C, treated with trimethyl borate (27.4 ml, 244 mmol), warmed to room temperature, treated with MeOH (100 mL) and water (5 mL), stirred at room temperature for 30 min and concentrated *in vacuo*. The residue was treated with MeOH (3 x 100 mL) and concentrated *in vacuo* after each addition to give the boronic ester as an orange gum. A solution of 2-amino-4,6-dichloorpyrimidine (20 g, 122 mmol) in THF (1 L) was treated with sat.$NaHCO_3$ (250 mL), a solution of the above boronic ester (122 mmol) in THF (50 mL) and tetrakis(triphenylphosphine)palladium (6.93 g, 6 mmol), stirred at 70 °C for 20 h, cooled, extracted with EtOAc (2 x 100 mL), washed with water (200 mL) and the combined organic phase dried ($MgSO_4$) and concentrated *in vacuo* to

give the product (24.536 g, 96 %) as a yellow solid; NMR δ_H (400 MHz, DMSO) 2.37 (3H, s), 6.32 – 6.33 (1H, m), 6.89 (1H, s), 7.11 (2H, s), 7.18 – 7.19 (1H, m).

Method AC

6-(Tert-butyldimethylsilyloxymethyl)pyridine-2-methanamine

A solution of 6-aminomethypyridine-2-methanol (5 g, 36.2 mmol) in anhydrous DMF (25 ml) at 0°C was treated with t-butyldimethylsilyl chloride (5.728 g, 38 mmol) and imidazole (2.584g, 38 mmol). The reaction was stirred at room temperature for 20 h, poured into 1.5M NaOH(aq) and extracted with EtOAc, washed with water x 4 and brine x 2. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give the product as a yellow oil; NMR δ_H (400 MHz, $CDCl_3$) 0.82 (9H, s), 0.87 (6H, s), 1.81 (2H, s), 3.84 (2H, s), 4.73 (2H, s), 7.03 (1H, d, *J* 8.0 Hz), 7.28 (1H, d, *J* 7.5 Hz), 7.57 (1H, t, *J* 8.0 Hz); M/Z Found M+1 = 253

Method AD

2-Amino-6-(5-methyl-2-furyl)-*N*-(6-hydroxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide (Example 133)

A solution of 2-amino-6-(5-methyl-2-furyl)-*N*-(6-(tert-butyldimethylsilyloxymethyl)pyridin-2-ylmethyl)pyrimidine-4-carboxamide (614 mg, 1.36 mmol) in acetic acid:water:THF (3:1:1) was stirred at room temperature for 4 days. The reaction was neutralised with saturated $NaHCO_3$(aq) and extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*, isolated by filtration and washed with MeOH to give the product (536 mg, 49%) as a cream solid.

Method AE

2-Amino-5-chloro-*N*-(6-methoxymethyl-2-pyridylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide (Example 116)

N-Chlorosuccinimide (24 mg, 0.156 mmol) was added to a solution of X (50 mg, 0.142 mmol) in acetic acid (10 ml) at room temperature. The mixture was then stirred at 100 °C for 2 h. After cooling to room temperature the solvent was evaporated and the residue was partitioned between ethyl acetate and sat. aq. $NaHCO_3$ .The organic portion was dried and

evaporated, the residue was triturated with diethyl ether and the resulting solid was filtered off to give X (30 mg, 54%).

Method AF

2-Amino-5-bromo-*N*-(6-methoxymethyl-2-pyridylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide (Example 117)

N-Bromosuccinimide (28 mg, 0.156 mmol) was added to a solution of X (50 mg, 0.142 mmol) in acetic acid at room temperature and the mixture was stirred for 2 h. The solvent was evaporated and the residue partitioned between ethyl acetate and sat. aq. $NaHCO_3$ .The organic portion was dried and evaporated, the residue was triturated with diethyl ether and the resulting solid was filtered off to give X (50 mg, 82%).

Table 2

Example	Method	Yield (%)	Physical Data
1	D	26	mp 200.0 – 205.9 °C; IR ν_{max} (DR)/cm^{-1} 3374, 3209, 2107, 1676, 1636, 1541, 1489, 1232; NMR δ_H (400 MHz, DMSO) 4.55 (2H, d, *J* 6.0 Hz), 6.71 (1H, s), 6.90 (2H, s), 7.10 – 7.49 (6H, m), 7.94 (1H, s), 8.79 (1H, t, *J* 5.5 Hz); LC 3.7 min. (50/80).
2	D	23	IR ν_{max} (DR)/cm^{-1} 3318, 3210, 1686, 1644, 1557, 1471, 1215; NMR δ_H (400 MHz, DMSO) 6.73 (1H, s), 6.98 (2H, s), 7.34 (1H, s), 7.46 (2H, s), 7.62 (1H, s), 7.90 – 8.05 (2H, m), 10.53 (1H, s); LC 5.8 min. (50/80).
3	D	36	mp 229.2 – 234.5 °C; IR ν_{max} (DR)/cm^{-1} 4004, 3465, 3368, 3204, 3091, 2930, 2832, 1675, 1592, 1354, 1252; NMR δ_H (400 MHz, DMSO) 3.74 (3H, s), 4.47 (2H, s), 6.71 (1H, s), 6.72 – 7.10 (5H, m), 7.18 – 7.36 (2H, m), 7.41 (1H, s), 7.94 (1H, s), 8.78 (1H, s); LC 3.4 min. (50/80).
4	D	4	IR ν_{max} (DR)/cm^{-1} 3329, 3193, 2936, 1633, 1539, 1471, 1224; NMR δ_H (400 MHz, DMSO) 2.93 (3H, s), 2.97 (3H, s), 6.67 – 6.70 (1H, m), 6.86 (2H, s), 6.90 (1H, s), 7.24 (1H, d, *J* 3.5 Hz), 7.88 – 7.91 (1H, m); LC 1.25 min. (50/80).
5	D	13	mp 139.5 – 143.0 °C; IR ν_{max} (DR)/cm^{-1} 3331, 3212, 2937, 2858, 1627, 1539, 1471, 1264, 1216; NMR δ_H (400 MHz, DMSO) 1.43 – 1.67 (6H, m), 3.24 – 3.30 (2H, m), 3.55 (2H, t, *J* 5.5 Hz), 6.68 – 6.70 (1H, m), 6.88 (1H, s), 6.89 (2H, s), 7.25 (1H, dd, *J* 3.5, 1.0 Hz), 7.89 – 7.91 (1H, m); LC 1.1 min. (50/80).

6	D	19	IR ν_{max} (DR)/cm^{-1} 3361, 3196, 2956, 2835, 1674, 1538, 1248; NMR δ_H (400 MHz, DMSO) 4.47 (2H, d, *J* 6.5 Hz), 6.69 – 6.73 (1H, m), 6.86 – 6.97 (3H, m), 7.02 (1H, d, *J* 7.5 Hz), 7.20 (1H, dd, *J* 7.5, 2.0 Hz), 7.24 – 7.31 (2H, m), 7.41 (1H, s), 7.92 – 7.96 (1H, m), 8.56 (1H, t, *J* 6.5 Hz); LC 4.5 min. (50/80).
7	D	12	IR ν_{max} (DR)/cm^{-1} 3381, 3201, 2923, 1681, 1555, 1342, 1255; NMR δ_H (400 MHz, DMSO) 4.50 (2H, d, *J* 6.0 Hz), 6.27 – 6.35 (1H, m), 6.40 (1H, s), 6.71 (1H, s), 6.89 (2H, s), 7.29 (1H, d, *J* 3.5 Hz), 7.40 (1H, s), 7.58 (1H, s), 7.93 (1H, s), 8.63 (1H, t, *J* 6.0 Hz); LC 1.8 min. (50/80).
8	D	15	mp 218.0 – 219.8 °C; IR ν_{max} (DR)/cm^{-1} 3443, 3193, 1698, 1599, 1486, 1322, 1245; NMR δ_H (400 MHz, DMSO) 6.68 – 6.72 (1H, m), 6.84 (2H, s), 7.27 (1H, d, *J* 3.5 Hz), 7.39 (1H, s), 7.72 (2H, d, *J* 10.5 Hz), 7.91 – 7.94 (1H, m); LC 0.6 min. (50/80).
9	D	37	mp 202.4 – 202.9 °C; IR ν_{max} (DR)/cm^{-1} 3366, 3192, 2872, 1637, 1509, 1351, 1218; NMR δ_H (400 MHz, DMSO) 2.86 (6H, s), 4.36 (2H, d, *J* 6.0 Hz), 6.66 – 6.72 (3H, m), 6.89 (2H, s), 7.13 – 7.19 (2H, m), 7.29 (1H, dd, *J* 3.5, 1.0 Hz), 7.41 (1H, s), 7.93 – 7.95 (1H, m), 8.52 (1H, t, *J* 6.0 Hz); LC 3.1 min. (50/80).
10	D	35	mp 108.2 – 117.4 °C; IR ν_{max} (DR)/cm^{-1} 4005, 3336, 2929, 2101, 1633, 1228; NMR δ_H (400 MHz, DMSO) 3.38 (3H, s), 4.51 (2H, s), 4.59 (2H, d, *J* 6.0 Hz), 6.70 – 6.73 (1H, m), 7.24 (1H, d, *J* 7.5 Hz), 7.29 – 7.33 (2H, m), 7.43 (1H, s), 7.79 (1H, t, *J* 8.0 Hz), 7.93 – 7.95 (1H, m), 8.98 (1H, t, *J* 6.0 Hz); LC 1.1 min. (50/80).
11	D	35	mp 200.2 – 200.3 °C; IR ν_{max} (DR)/cm^{-1} 3347, 1646, 1503, 1246; NMR δ_H (400 MHz, DMSO) 2.33 (3H, s), 4.63 (2H, d, *J* 5.0 Hz), 6.70 – 6.73 (1H, m), 7.01 (2H, s), 7.27 (1H, dd, *J* 7.5, 4.5 Hz), 7.31 (1H, d, *J* 3.5 Hz), 7.46 (1H, s), 7.64 (1H, dt, *J* 7.5, 1.0 Hz), 7.94 – 7.96 (1H, m), 8.41 (1H, dd, *J* 4.5, 1.0 Hz); LC 1.5 min. (50/80).
12	D	39	IR ν_{max} (DR)/cm^{-1} 3413, 3097, 2931, 1635, 1550, 1261; NMR δ_H (400 MHz, DMSO) 2.89 (3H, s), 2.97 (3H, s), 4.52 (2H, d, *J* 6.0 Hz), 6.69 – 6.73 (1H, m), 6.88 (2H, s), 7.25 – 7.32 (2H, m), 7.34 (1H, s), 7.36 – 7.44 (3H, m), 7.94 (1H, s), 8.92 (1H, t, *J* 6.0 Hz); LC 0.9 min. (50/80).
13	D	44	mp 209.1 – 209.2 °C; IR ν_{max} (DR)/cm^{-1} 3380, 3107, 1681, 1651, 1514, 1485, 1230; NMR δ_H (400 MHz, DMSO) 4.62 (2H, d, *J* 6.0 Hz), 6.68 – 6.75 (1H, m), 6.94 (2H, s), 7.26 – 7.33 (2H, m), 7.35 (1H, d, *J* 7.5 Hz), 7.43 (1H, s), 7.78 (1H, dt, *J* 7.5, 1.5 Hz), 7.94 (1H, s), 8.54 (1H, d, *J* 4.5 Hz), 8.96 (1H, t, *J* 6.0 Hz); LC 5.4 min. (20/50).
14	D	41	mp 195.4 – 196.3 °C; IR ν_{max} (DR)/cm^{-1} 3328, 2937, 1519, 1416, 1353, 1217; NMR δ_H (400 MHz, DMSO) 4.51 (2H, d, *J* 6.5 Hz), 6.70 – 6.72 (1H, m), 6.87 (2H, s), 7.27 – 7.31 (3H, m), 7.41 (1H, s), 7.94 (1H, d, *J* 1.0 Hz), 8.48 – 8.52 (2H, m), 9.03 (1H, t, *J* 6.0 Hz); LC 5.2 min. (20/50).
15	D	46	mp 151.1 – 152.2 °C; IR ν_{max} (DR)/cm^{-1} 3377, 3201, 2918, 1681, 1519, 1355, 1221; NMR δ_H (400 MHz, DMSO) 2.31 (3H, s), 4.49 (2H, d, *J* 6.0 Hz), 6.70 – 6.72 (1H, m), 6.91 (2H, s), 7.14 – 7.21 (3H, m), 7.22 – 7.27 (1H, m), 7.30 (1H, d, *J* 3.5 Hz), 7.42 (1H, s), 7.93 – 7.95 (1H, m), 8.59 (1H, t, *J* 6.0 Hz); LC 3.8 min. (50/80).

16	D	50	mp 170.6 – 170.7 °C; IR ν_{max} (DR)/cm^{-1} 3487, 3316, 2919, 1633, 1520, 1333; NMR δ_H (400 MHz, DMSO) 4.57 (2H, d, *J* 6.0 Hz), 6.70 – 6.72 (1H, m), 6.87 (2H, s), 7.30 (1H, dd, *J* 3.5, 1.0 Hz), 7.41 (1H, s), 7.55 – 7.66 (3H, m), 7.69 (1H, s), 7.93 – 7.95 (1H, m), 9.04 (1H, t, *J* 6.5 Hz); LC 4.9 min. (50/80).
17	D	38	mp 290.9 – 291.3 °C; IR ν_{max} (DR)/cm^{-1} 3425, 3277, 1671, 1599, 1510, 1459, 1323, 1202; NMR δ_H (400 MHz, DMSO) 4.74 (2H, d, *J* 6.0 Hz), 6.70 – 6.74 (1H, m), 6.95 (2H, s), 7.11 – 7.19 (2H, m), 7.31 (1H, d, *J* 3.5 Hz), 7.42 – 7.60 (3H, m), 7.95 (1H, d, *J* 1.5 Hz), 8.92 (1H, t, *J* 6.0 Hz), 12.30 (1H, s); LC 1.8 min. (50/80).
18	D	35	mp 162.0 – 170.0 °C; IR ν_{max} (DR)/cm^{-1} 3197, 2216, 1633, 1513, 1352, 1219; NMR δ_H (400 MHz, DMSO) 4.51 (2H, d, *J* 6.5 Hz), 6.69 – 6.73 (1H, m), 6.86 (2H, s), 7.29 (1H, d, *J* 3.0 Hz), 7.36 (1H, dd, *J* 7.5, 4.5 Hz), 7.40 (1H, s), 7.73 (1H, d, *J* 7.5 Hz), 7.94 (1H, s), 8.47 (1H, d, *J* 4.0 Hz), 8.56 (1H, s), 8.98 (1H, t, *J* 6.0 Hz); LC 5.3 min. (20/50).
19	D	13	mp 143.2 – 143.7 °C; IR ν_{max} (DR)/cm^{-1} 3324, 3210, 2922, 1673, 1633, 1520, 1342, 1249; NMR δ_H (400 MHz, DMSO) 2.29 (3H, s), 4.45 (2H, d, *J* 6.0 Hz), 6.68 – 6.74 (1H, m), 6.88 (2H, s), 7.04 – 7.17 (3H, m), 7.22 (1H, t, *J* 7.5 Hz), 7.29 (1H, d, *J* 3.0 Hz), 7.42 (1H, s), 7.94 (1H, s), 8.76 (1H, t, *J* 6.0 Hz); LC 3.9 min. (50/80).
20	D	14	NMR δ_H (400 MHz, DMSO) 3.36 (3H, s), 4.56 (2H, s), 4.67 (2H, d, *J* 5.5 Hz), 6.70 – 6.73 (1H, m), 6.99 (2H, s), 7.30 (1H, dd, *J* 3.5, 1.0 Hz), 7.36 (1H, dd, *J* 7.5, 5.0 Hz), 7.45 (1H, s), 7.79 (1H, dd, *J* 7.5, 1.5 Hz), 7.93 – 7.95 (1H, m), 8.52 (1H, dd, *J* 4.5, 2.0 Hz), 8.99 (1H, t, *J* 5.0 Hz); M/Z 340 $(M+H)^+$; LC 1.2 min. (50/80).
21	D	7	IR ν_{max} (DR)/cm^{-1} 3509, 3346, 2814, 2764, 1667, 1589, 1503, 1338, 1239; NMR δ_H (400 MHz, DMSO) 2.19 (6H, s), 3.49 (2H, s), 4.75 (2H, d, *J* 5.5 Hz), 6.70 – 6.72 (1H, m), 6.94 (2H, s), 7.29 (1H, d, *J* 3.5 Hz), 7.33 (1H, dd, *J* 7.0, 4.5 Hz), 7.44 (1H, s), 7.70 (1H, d, *J* 7.0 Hz), 7.93 – 7.96 (1H, m), 8.49 (1H, d, *J* 3.5 Hz), 9.20 (1H, t, *J* 5.0 Hz); LC 1.1 min. (50/80).
22	D	34	mp 195.5 – 197.5 °C; IR ν_{max} (DR)/cm^{-1} 3314, 2821, 1675, 1633, 1543, 1345, 1226, 1114; NMR δ_H (400 MHz, DMSO) 2.39 (4H, t, *J* 4.5 Hz), 3.55 – 3.59 (6H, m), 4.78 (2H, d, *J* 5.0 Hz), 6.70 – 6.73 (1H, m), 6.97 (2H, s), 7.30 (1H, dd, *J* 3.5, 1.0 Hz), 7.33 (1H, dd, *J* 7.5, 5.0 Hz), 7.45 (1H, s), 7.72 (1H, dd, *J* 7.5, 2.0 Hz), 7.94 – 7.96 (1H, m), 8.49 (1H, dd, *J* 4.5, 2.0 Hz), 9.00 (1H, t, *J* 5.0 Hz); LC 1.3 min. (50/80).
23	D	28	IR ν_{max} (DR)/cm^{-1} 3353, 3207, 2975, 1643, 1502, 1243; NMR δ_H (400 MHz, DMSO) 2.27 (3H, s), 2.51 (3H, s), 4.56 (2H, d, *J* 4.5 Hz), 6.71 – 6.72 (1H, m), 7.02 (2H, s), 7.12 (1H, d, *J* 8.0 Hz), 7.31 (1H, dd, *J* 3.5, 1.0 Hz), 7.45 (1H, s), 7.51 (1H, d, *J* 7.5Hz), 7.94 – 7.96 (1H, m), 9.11 (1H, t, *J* 5.0 Hz); LC 2.1 min. (50/80).
24	D	17	IR ν_{max} (DR)/cm^{-1} 3509, 3366, 2920, 1750, 1682, 1519, 1418, 1356, 1229; NMR δ_H (400 MHz, DMSO) 4.60 (2H, d, *J* 6.0 Hz), 6.70 – 6.73 (1H, m), 6.94 (2H, s), 7.17 (1H, dd, *J* 5.0, 3.5 Hz), 7.30 (1H, d, *J* 3.5 Hz), 7.43 (2H, s), 7.66 (1H, dd, *J* 3.5, 1.0 Hz), 7.72 (1H, dd, *J* 5.0, 1.0 Hz), 7.94 – 7.97 (1H, m), 8.84 (1H, t, *J* 6.0 Hz); LC 3.6 min. (50/80).

25	D	15	IR ν_{max} (DR)/cm^{-1} 3354, 3191, 1678, 1635, 1514, 1328, 1256, 1231; NMR δ_H (400 MHz, DMSO) 4.65 (2H, d, *J* 6.0 Hz), 6.70 – 6.73 (1H, m), 6.90 (2H, s), 6.97 (1H, dd, *J* 5.0, 3.5 Hz), 7.03 – 7.06 (1H, m), 7.29 – 7.31 (1H, m), 7.39 – 7.42 (1H, m), 7.41 (1H, s), 7.94 – 7.95 (1H, m), 8.88 (1H, t, *J* 6.5 Hz); LC 1.9 min. (50/80).
26	D	17	IR ν_{max} (DR)/cm^{-1} 3474, 3353, 3203, 1687, 1628, 1521, 1367, 1217; NMR δ_H (400 MHz, DMSO) 4.66 (2H, d, *J* 6.0 Hz), 6.70 – 6.73 (1H m), 6.91 (2H, s), 7.06 (1H, d, *J* 4.0 Hz), 7.22 – 7.26 (1H, m), 7.31 (1H, dd, *J* 3.5, 1.0 Hz), 7.42 (1H, s), 7.63 (1H, d, *J* 4.0 Hz), 7.77 – 7.88 (2H, m), 7.94 – 7.96 (1H, m), 8.46 – 8.50 (1H, m), 8.97 (1H, t, *J* 6.0 Hz); LC 2.7 min. (50/80).
27	D	19	IR ν_{max} (DR)/cm^{-1} 3491, 3321, 1659, 1527, 1455, 1318; NMR δ_H (400 MHz, DMSO) 2.29 (3H, s), 4.42 (2H, d, *J* 6.0 Hz), 6.28 (1H, s), 6.70 – 6.73 (1H, m), 6.89 (2H, s), 7.30 (1H, dd, *J* 3.5, 1.0 Hz), 7.40 (1H, s), 7.94 – 7.96 (1H, m), 8.89 (1H, t, *J* 6.0 Hz); LC 4.4 min. (50/80).
28	D	17	IR ν_{max} (DR)/cm^{-1} 3460, 3319, 1679, 1520, 1398, 1360, 1217; NMR δ_H (400 MHz, DMSO) 2.37 (3H, s), 4.49 (2H, d, *J* 6.0 Hz), 6.17 (1H, s), 6.70 – 6.73 (1H, m), 6.91 (2H, s), 7.30 (1H, d, *J* 3.5 Hz), 7.40 (1H, s), 7.94 – 7.96 (1H, m), 8.89 (1H, t, *J* 6.0 Hz); LC 1.0 min. (50/80).
29	D	27	mp 178.0 – 178.1 °C; IR ν_{max} (DR)/cm^{-1} 3317, 3211, 1635, 1543, 1466, 1360, 1250; NMR δ_H (400 MHz, DMSO) 2.37 (3H, s), 3.91 (3H, s), 4.39 (2H, d, *J* 6.0 Hz), 6.70 – 6.72 (1H, m), 6.81 (1H, d, *J* 7.5 Hz), 6.93 (2H, s), 7.30 (1H, d, *J* 3.5 Hz), 7.40 (1H, s), 7.43 (1H, d, *J* 7.5 Hz), 7.93 – 7.95 (1H, m), 8.67 (1H, t, *J* 6.0 Hz); LC 2.8 min. (50/80).
30	D	14	IR ν_{max} (DR)/cm^{-1} 3335, 2862, 1674, 1515, 1339, 1223; NMR δ_H (400 MHz, DMSO) 4.44 (2H, d, *J* 6.0 Hz), 4.89 (2H, s), 5.32 (2H, s), 6.71 – 6.72 (1H, m), 6.84 – 7.00 (4H, m), 7.30 (1H, dd, *J* 3.5, 1.0 Hz), 7.40 (1H, s), 7.93 – 7.96 (1H, m), 8.75 (1H, t, *J* 6.0 Hz); LC 2.9 min. (50/80).
31	M	13	M/Z 310 $(M+H)^+$; LC 1.0 min. (50/80)
32	M	65	IR ν_{max} (DR)/cm^{-1} 3359, 3184, 2917, 1633, 1538, 1471, 1224 and 747; NMR δ_H (400 MHz, DMSO) 10.80 (1H, br s), 8.46 (1H, t, *J* 6.0 Hz), 7.94 (1H, t, *J* 1.5 Hz), 7.60 (1H, t, *J* 7.5 Hz), 7.41 (1H, s), 7.34 (1H, d, *J* 8.0 Hz), 7.29 (1H, dd, *J* 3.5, 1.0 Hz), 7.19 (1H, d, *J* 2.0 Hz), 7.10-7.04 (1H, m), 7.01-6.96 (1H , m), 6.86 (2H, br s), 6.71 (1H, dd, *J* 3.5, 1.5 Hz), 3.60 (2H, dd, *J* 6.5 Hz) and 2.95 (2H, t, *J* 7.5 Hz); M/Z 348 $(M+H)^+$; LC 3.4 min. (50/80).
33		61	mp 183.4 – 183.6 °C; M/Z 327 $(M+H)^+$; LC 4.8 min. (20/50).

34			LC 3.7 min. (20/50)
35	J	59	Mp 170.1 - 170.5 °C; IR ν_{max} (DR)/cm^{-1} 3491, 3299, 1627, 1519, 1238 and 771; NMR δ_H (400 MHz, DMSO) 11.04 (1H, br s), 8.59 (1H, t, *J* 6.0 Hz), 7.95-7.93 (1H, m), 7.52-7.49 (1H, m), 7.43 (1H, s), 7.35 (1H, d, *J* 8.5 Hz), 7.32 (1H, t, *J* 3.0 Hz), 7.29 (1H, d, *J* 3.5 Hz), 7.08 (1H, dd, *J* 8.5 Hz, 1.5 Hz), 6.89 (2H, br s), 6.71 (1H, dd, *J* 3.5, 1.5 Hz), 6.41-6.37 (1H, m) and 4.55 (2H, d, *J* 6.0 Hz); M/Z 334 $(M+H)^+$; LC 2.7 min. (50/80).
36	J	54	Mp 155.9 - 156.0 °C; IR ν_{max} (DR)/cm^{-1} 3325, 2917, 1594, 1517, 1237 and 747; NMR δ_H (400 MHz, DMSO) 10.61 (1H, br s), 8.52 (1H, t, *J* 6.0 Hz), 7.95-7.92 (1H, m), 7.43 (1H, s), 7.33 (1H, br s), 7.29 (1H, d, *J* 3.5 Hz), 7.18 (1H, d, *J* 8.5 Hz), 6.98 (1H, dd, *J* 8.5, 2.0 Hz), 6.90 (2H, br s), 6.71 (1H, dd, *J* 3.5, 2.0 Hz), 4.53 (3H, s), 2.29 (3H, s) and 2.13 (3H, s); M/Z 362 $(M+H)^+$; LC 4.9 min. (50/80).
37	J	33	Mp 191.8 - 192.2 °C ; NMR δ_H (400 MHz, DMSO) 9.04 (1H, t, *J* 6.5 Hz), 7.97 (1H, d, *J* 8.5 Hz), 7.94 (1H, d, *J* 2.5 Hz), 7.42 (1H, br s), 7.41 (1H, s), 7.37 (1H, dd, *J* 8.5, 1.5 Hz), 7.30 (1H, d, *J* 3.5 Hz), 6.87 (2H, br s), 6.71 (1H, dd, *J* 3.5, 1.5 Hz), 4.55 (2H, d, *J* 6.0 Hz) and 3.30 (3H, s); M/Z 354 $(M+H)^+$; LC 3.8 min. (50/80).
38	J		LC 2.0 min. (50/80).
39	J	6	M/Z 324 $(M+H)^+$; LC 2.3 min. (20/50).
40	J	60	Mp 105.6 - 105.7 °C; IR ν_{max} (DR)/cm^{-1} 3332, 2924, 1747, 1594, 1519, 1228 and777; NMR δ_H (400 MHz, DMSO) 10.85 (1H, br s), 8.55 (1H, t, *J* 6.0 Hz), 7.95-7.93 (1H, m), 7.43 (1H, s), 7.35 (1H, br s), 7.29 (1H, d, *J* 3.5 Hz), 7.22 (1H, d, *J* 8.5 Hz), 6.98 (1H, dd, *J* 8.0, 1.5 Hz), 6.89 (2H, br s), 6.71 (1H, dd, *J* 3.5, 2.0 Hz), 6.08 (1H, s), 4.51 (2H, d, *J* 6.0 Hz) and 2.36 (3H, s); M/Z 348 $(M+H)^+$; LC 3.6 min. (50/80)
41		28	mp 155.2 – 155.7 °C, M/Z 411 $(M+H)^+$; LC 1.5 min. (50/80).
42	K	35	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 4.50 (2H, d, *J* 6.3 Hz), 6.71 (1H, dd, *J* 1.6, 3.3 Hz), 6.88 (2H, br s), 7.26 – 7.34 (6H, m), 7.94 (1H, m) and 8.81 (1H, t, *J* 6.1 Hz); M/Z 295 $(M+H)^+$; LC 2.3 min. (50/80)

43	J	71	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 3.92 (2H, dt, *J* 1.6, 5.7 Hz), 5.15 (2H, m), 5.90 (1H, dq, *J* 5.2, 17.2 Hz), 6.71 (1H, dd, *J* 1.9, 3.5 Hz), 6.89 (2H, br s), 7.29 (1H, m), 7.39 (1H, s), 7.94 (1H, m) and 8.46 (1H, t, *J* 6.0 Hz); M/Z 245 $(M+H)^+$; LC 1.0 min. (50/80).
44	J	40	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 1.08 (3H, d, *J* 6.2 Hz), 3.15 (1H, m, *J* 5.6 Hz), 3.37 (1H, dq, *J* 4.4, 6.6 Hz), 3.78 (1H, m), 4.87 (1H, d, *J* 4.7 Hz), 6.71 (1H, dd, *J* 1.8, 3.5 Hz), 6.96 (2H, br s), 7.29 (1H, d, *J* 3.5 Hz), 7.41 (1H, s), 7.94 (1H, d, *J* 1.1 Hz) and 8.26 (1H, t, *J* 1.9 Hz); M/Z 263 $(M+H)^+$; LC 2.7 min. (20/50).
45		31	mp 200.4 – 202.0 °C; M/Z 464 $(M+H)^+$; LC 1.3 min. (50/80).
46	J	6	Mp 148 – 148.4 °C; M/Z 354 $(M+H)^+$; LC 1.8 min. (50/80).
47	K	63	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 3.67 (3H, s), 4.09 (2H, d, *J* 6.1 Hz), 6.71 (1H, dd, *J* 1.9, 3.5 Hz), 6.93 (2H, br s), 7.30 (1H, m), 7.40 (1H, s), 7.94 (1H, m) and 8.71 (1H, t, *J* 6.1 Hz); M/Z 277 $(M+H)^+$; LC 3.6 min. (20/50).
48	J	46	Mp 193.8 - 194.0 °C; IR ν_{max} (DR)/cm^{-1} 3328, 1536, 1348, 1239, 729 and 672; NMR δ_H (400 MHz, DMSO) 11.03 (1H, br s), 8.67 (1H, t, *J* 6.5 Hz), 7.95-7.93 (1H, m), 7.49 (1H, d, *J* 8.0 Hz), 7.43 (1H, s), 7.36 (1H, br s), 7.33-7.27 (2H, m), 6.98 (1H, dd, *J* 8.0, 1.5 Hz), 6.89 (2H, br s), 6.71 (1H, dd, *J* 3.0, 1.5 Hz), 6.41-6.37 (1H, m) and 4.57 (2H, d, *J* 6.0 Hz); M/Z 334 $(M+H)^+$; LC 2.9 min. (50/80)
49	J	28	Mp 230.7 - 230.9 °C; IR ν_{max} (DR)/cm^{-1} 3408, 3190, 1652, 1504, 1246, 788 and 754; NMR δ_H (400 MHz, DMSO) 9.02 (1H, dd, *J* 4.0, 1.5 Hz), 8.98 (1H, t, *J* 6.5 Hz), 8.42 (1H, dd, *J* 8.5, 2.0 Hz), 7.96-7.90 (2H, m), 7.69 (1H, d, *J* 7.0 Hz), 7.64-7.54 (2H, m), 7.43 (1H, s), 7.29 (1H, d, *J* 3.5 Hz), 6.89 (2H, br s), 6.70 (1H, dd, *J* 3.5, 1.5 Hz) and 5.12 (2H, d, *J* 6.5 Hz); M/Z 346 $(M+H)^+$; LC 2.7 min. (50/80).
50	J	72	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 3.01 (2H, t, *J* 7.0 Hz), 3.67 (2H, dd, *J* 7.0, 13.2 Hz), 6.71 (1H, m), 6.87 (2H, br s), 7.22 – 7.30 (4H, m), 7.38 (1H, s), 7.72 (1H, dt, *J* 1.8, 3.7 Hz), 7.93 (1H, m), 8.55 (1H, d, *J* 5.2 Hz) and 8.61 (1H, t, *J* 6.0 Hz); M/Z 310 $(M+H)^+$; LC 1.0 min. (50/80).
51	J	85	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 4.58 (2H, d, *J* 6.4 Hz), 6.71 (1H, dd, *J* 1.6, 3.0 Hz), 6.92 (2H, br s), 7.30 – 7.37 (4H, m), 7.42 (1H, s), 7.47 (1H, dd, *J* 1.6, 7.0 Hz), 7.94 (1H, m) and 8.83 (1H, t, *J* 6.4 Hz); M/Z 329 $(M+H)^+$; LC 3.8 min. (50/80).
52	J	86	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 4.69 (2H, d, *J* 6.0 Hz), 6.71 (1H, dd, *J* 1.6, 3.6 Hz), 6.91 (2H, br s), 7.30 (1H, d, *J* 3.6 Hz), 7.42 (1H, s), 7.50 (1H, q, *J* 7.6 Hz), 7.66 (1H, t, *J* 7.6 Hz), 7.75 (1H, d, *J* 7.6 Hz), 7.94 (1H, m) and 8.92 (1H, t, *J* 6.0 Hz); M/Z 363 $(M+H)^+$; LC 4.3 min. (50/80).

53	J	34	Mp 171.2 - 172.1 °C; IR ν_{max} (DR)/cm^{-1} 3336, 3220, 1520, 1232, 828 and 772; NMR δ_H (400 MHz, DMSO) 9.11 (1H, t, *J* 6.0 Hz), 8.07 (1H, d, *J* 9.0 Hz), 7.43 (1H, s), 7.30 (1H, d, *J* 3.5 Hz), 6.88 (2H, br s), 6.71 (1H, dd, *J* 3.5, 1.5 Hz) and 4.70 (2H, d, *J* 6.0 Hz); M/Z 353 $(M+H)^+$; LC 2.6 min. (50/80).
54		58	NMR δ_H (400 MHz, DMSO) 2.86 – 2.92 (6H, m), 4.60 (2H, d, *J* 6.0Hz), 5.13 (2H, s), 6.70 – 6.71(1H, m), 6.90 (2H, s), 7.26 (2H, d, *J* 7.5Hz), 7.29 (1H, d, *J* 3.5), 7.42 (1H, s), 7.80 (1H, t, *J* 8.0Hz), 7.93 (1H, s), 8.98 (1H, t, *J* 5.0Hz); LC 1.1 min. (50/80).
55	J	2	M/Z 346 $(M+H)^+$; LC 2.4 min. (50/80).
56	J	80	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 3.50 (4H, m), 3.60 (2H, m), 3.71 (2H, m), 6.66 – 6.70 (2H, m), 6.84 (1H, d, *J* 8.7 Hz), 6.94 (2H, br s), 6.98 (1H, s), 7.26 (1H, d, *J* 3.6 Hz), 7.55 (1H, m), 7.91 (1H, m) and 8.13 (1H, dd, *J* 1.8, 5.2 Hz); M/Z 351 $(M+H)^+$; LC 1.0 min. (50/80).
57	J	40	Mp 180.9 - 1 81.4 °C; IR ν_{max} (DR)/cm^{-1} 3393, 3202, 1686, 1643, 1517, 1243 and 753; NMR δ_H (400 MHz, DMSO) 9.24 (1H, d, *J* 6.0), 8.36 (1H, d, *J* 8.5 Hz), 8.07 (1H, d, *J* 8.5 Hz), 7.97 (1H, dd, *J* 8.0, 1.0 Hz), 7.95-7.93 (1H, m), 7.80-7.75 (1H, m), 762-7.57 (1H, m), 7.53 (1H, d, *J* 8.5 Hz), 7.46 (1H, s), 7.31 (1H, d, *J* 3.5 Hz), 6.96 (2H, br s), 6.71 (1H, dd, *J* 3.5, 1.5 Hz) and 4.81 (2H, d, *J* 6.0 Hz); M/Z 346 $(M+H)^+$; LC 2.4 min. (50/80).
58	J	41	Mp 219.9 - 222.3 °C; IR ν_{max} (DR)/cm^{-1} 3318, 2911, 1667, 1518, 1247 and 1129; NMR δ_H (400 MHz, DMSO) 9.34 (1H, t, *J* 6.2 Hz), 8.06 (1H, d, *J* 8.0 Hz), 8.0-7.92 (2H, m), 7.54-7.47 (1H, m), 7.46-7.39 (2H, m), 7.32 (1H, d, *J* 3.5 Hz), 6.93 (2H, br s), 6.72 (1H, dd, *J* 3.5, 2.0 Hz) and 4.91 (2H, d, *J* 6.0 Hz); M/Z 352 $(M+H)^+$; LC 2.6 min. (50/80).
59	J	35	Mp 154.5 – 156.9 °C, M/Z 394 $(M+H)^+$; LC 4.1 min. (50/80).
60	J	67	Mp 158.7 – 158.9 °C, M/Z 309 $(M+H)^+$; LC 3.3 min. (50/80).
61	J	71	Mp 171.2 - 172.7 °C; IR ν_{max} (DR)/cm^{-1} 3490, 3362, 3172, 1634, 1516, 1234, 1018 and 734; NMR δ_H (400 MHz, DMSO) 8.91 (1H, t, *J* 6.5 Hz), 7.94 (1H, d, *J* 2.5 Hz), 7.42-7.32 (4H, m), 7.29 (1H, dd, *J* 3.5, 1.0 Hz), 6.87 (2H, br s), 6.71 (1H, dd, *J* 3.5, 1.5 Hz) and 4.48 (2H, d, *J* 6.0 Hz); M/Z 329 $(M+H)^+$; LC 4.5 min. (50/80).
62	J	65	Mp 176.2 - 177.3 °C; IR ν_{max} (DR)/cm^{-1} 3332, 3208, 1672, 1550, 1226, 838 and 734; NMR δ_H (400 MHz, DMSO) 8.86 (1H, t, *J* 6.5 Hz), 7.95-7.92 (1H, m), 7.41 (1H, s), 7.40-7.33 (2H, m), 7.29 (1H, dd, *J* 3.5, 1.0 Hz), 7.20-7.11 (2H, m), 6.87 (2H, br s), 6.71 (1H, dd, *J* 3.5, 2.0 Hz) and

			4.47 (2H, d, *J* 6.5 Hz); M/Z 313 $(M+H)^+$; LC 2.9 min. (50/80).
63	J	73	Mp 158.8 – 159.1°C , M/Z 309 $(M+H)^+$; LC 3.2 min. (50/80).
64		7	M/Z 439 $(M+H)^+$; LC 1.1 min. (50/80).
65	J	62	Mp 149.4 - 150.4 °C; IR ν_{max} (DR)/cm^{-1} 3406, 3318, 3208, 1682, 1514, 1246, 1030 and 596; NMR δ_H (400 MHz, DMSO) 8.69 (1H, t, *J* 6.0 Hz), 7.95-7.92 (1H, m), 7.41 (1H, s), 7.29 (1H, dd, *J* 3.5, 1.0 Hz), 7.28-7.23 (2H, m), 6.93-6.84 (4H, m), 6.71 (1H, dd, *J* 3.5, 1.5 Hz), 4.42 (2H, d, *J* 6.0 Hz) and 3.73 (3H, s); M/Z 325 $(M+H)^+$; LC 2.5 min. (50/80).
66	J	68	Mp 226.2 - 226.3 °C; NMR δ_H (400 MHz, DMSO) 7.96-7.92 (1H, m), 7.44-7.38 (1H, m), 7.35-7.29 (3H, m), 7.28 (1H, d, *J* 3.5 Hz), 7.16 (1H, s), 7.01 (2H, br s), 6.71 (1H, dd, *J* 3.5, 2.0 Hz), 5.04 (2H, br s) and 4.86 (2H, br s); M/Z 307 $(M+H)^+$; LC 2.1 min. (50/80).
67	J	29	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 3.28 (3H, s), 3.47 (4H, m), 6.71 (1H, dd, *J* 1.6, 3.5 Hz), 6.93 (2H, br s), 7.29 (1H, d, *J* 3.5 Hz), 7.40 (1H, s), 7.94 (1H, m) and 8.30 (1H, m); M/Z 263 $(M+H)^+$; LC 3.5 min. (20/50).
68	J	32	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 4.31 (2H, d, *J* 5.9 Hz), 6.72 (1H, dd, *J* 1.8, 3.4 Hz), 6.90 (2H, br s), 7.32 (1H, d, *J* 3.3 Hz), 7.40 (1H, s), 7.95 (1H, m) and 9.08 (1H, t, *J* 5.8 Hz); M/Z 244 $(M+H)^+$; LC 3.8 min. (20/50).
69	J	61	Mp 182.0 - 1 82.1 °C; IR ν_{max} (DR)/cm^{-1} 3356, 3187, 1673, 1638, 1509, 1229 and 805; NMR δ_H (400 MHz, DMSO) 8.76 (1H, t, *J* 6.5 Hz), 7.95 (1H, t, *J* 1.0 Hz), 7.41 (1H, s), 7.3 (1H, d, *J* 3.514 Hz), 7.21 (2H, d, *J* 8.031 Hz), 7.14 (2H, d, *J* 8.031 Hz), 6.91 (2H, br s), 6.71 (1H, dd, *J* 3.5, 1.5 Hz), 4.44 (2H, d, *J* 6.0 Hz) and 2.28 (3H, s); M/Z 309 $(M+H)^+$; LC 4.2 min. (50/80).
70	J	50	Mp 191.9 – 192.0°C, M/Z 323 $(M+H)^+$; LC 3.7 min. (50/80).
71	J	61	Mp 193.3 - 193.6 °C; IR ν_{max} (DR)/cm^{-1} 3422, 3318, 1616, 1538, 1226, 776 and 746; NMR δ_H (400 MHz, DMSO) 7.92 (1H, d, *J* 4.5 Hz), 7.30-7.06 (5H, m), 7.02-6.93 (3H, m), 6.73-6.67 (1H, m), 4.76 (1H, s), 4.59 (1H, s), 3.83 (1H, t, *J* 6.0 Hz), 3.61 (1H, t, *J* 6.0 Hz) and 2.88 (2H, q, *J* 6.0 Hz); M/Z 321 $(M+H)^+$; LC 1.9 min. (50/80).

72	J	17	Mp 203.8 - 204.5 °C; IR ν_{max} (DR)/cm^{-1} 3486, 3314, 3202, 1644, 1538, 1224 and 742; NMR δ_H (400 MHz, DMSO) 7.91 (1H, s), 7.27-7.14 (2H, m), 7.12-6.85 (4H, br m), 6.72-6.66 (1H, m), 3.70 (2H, br s), 2.81 (2H, t, *J* 6.5 Hz) and 2.00-1.86 (2H, m); M/Z 321 $(M+H)^+$; LC 1.5 min. (50/80).
73	J	83	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 4.50 (2H, d, *J* 6.4 Hz), 6.72 (1H, m), 6.91 (2H, br s), 7.07 – 7.18 (3H, m), 7.30 (1H, d, *J* 3.6 Hz), 7.35 – 7.41, 2H, m), 7.95 (1H, m) and 8.96 (1H, t, *J* 6.4 Hz); M/Z 313 $(M+H)^+$; LC 3.2 min. (50/80).
74	J	84	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 4.49 (2H, d, *J* 6.4 Hz), 6.72 (1H, m), 6.91 (2H, br s), 7.28 – 7.41 (6H, m), 7.95 (1H, m) and 8.99 (1H, t, *J* 6.4 Hz); M/Z 329 $(M+H)^+$; LC 4.5 min. (50/80).
75	J	60	Mp 251.9 - 252.3 °C; IR ν_{max} (DR)/cm^{-1} 3196, 2981, 1633, 1485, 1239, 1002, 756 and 538; NMR δ_H (400 MHz, DMSO) 8.13 (1H, d, *J* 8.0 Hz), 7.93 (1H, d, *J* 1.0 Hz), 7.33-7.20 (3H, m), 7.14-7.06 (2H, m), 6.97 (2H, br s), 6.71 (1H, dd, *J* 3.5, 1.5 Hz), 4.16 (2H, t, *J* 8.5 Hz) and 3.14 (1H, dd, *J* 16.5, 8.0 Hz); M/Z 307 $(M+H)^+$; LC 2.3 min. (50/80).
76	J	86	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 2.33 (3H, s), 6.73 (1H, dd, *J* 1.6, 3.6 Hz), 6.96 – 7.02 (3H, m), 7.27 (1H, t, *J* 8.0 Hz), 7.33 (1H, m), 7.47 (1H, s), 7.58 – 7.62 (2H, m), 7.96 (1H, m) and 10.16 (1H, s);M/Z 295 $(M+H)^+$; LC 4.8 min. (50/80).
77	J	62	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 2.26 (3H, s), 6.73 (1H, dd, *J* 2.0, 3.6 Hz), 7.06 (2H, br s), 7.27 (1H, m), 7.35 (1H, m), 7.48 (1H, s), 7.75 (1H, m), 7.96 (1H, m), 8.31 (1H, m) and 10.20 (1H, s) ; M/Z 295 (M^+); LC 1.1 min. (50/80).
78	J	64	Mp 126.7 - 127.2 °C; IR ν_{max} (DR)/cm^{-1} 3326, 3206, 1634, 1520 and 750; NMR δ_H (400 MHz, DMSO) 8.45 (1H, d, *J* 8.5 Hz), 7.96-7.93 (1H, m), 7.45 (1H, s), 7.32-7.17 (5H, m), 6.91 (2H, br s), 6.71 (1H, dd, *J* 3.5, 2.0 Hz), 5.49 (1H, q, *J* 7.5 Hz), 3.06-2.96 (1H, m), 2.92-2.81 (1H, m), 2.55-2.43 (1H, m) and 2.04-1.92 (1H, m); M/Z 321 $(M+H)^+$; LC 4.2 min. (50/80).
79	J	50	Mp 111.8 - 112.5 °C; IR ν_{max} (DR)/cm^{-1} 3205, 2940, 1706, 1651, 1537, 1269, 1014 and 748; NMR δ_H (400 MHz, DMSO) 11.81 (1H, s), 8.45 (1H, d, *J* 9.0 Hz), 7.95 (1H, d, *J* 1.0 Hz), 7.45 (1H, s), 7.32-7.17 (4H, m), 6.91 (2H, br s), 6.72 (1H, d, *J* 3.5 Hz), 5.49 (1H, dd, *J* 16.0, 7.5 Hz), 3.06-2.97 (1H, m), 2.92-2.81 (1H, m), 2.55-2.45 (1H, m) and 2.04-1 .92 (1H, m); M/Z 321 $(M+H)^+$; LC 4.1 min. (50/80).
80		16	M/Z 437 $(M+H)^+$; LC 2.8 min. (50/80).
81		2	M/Z 423 $(M+H)^+$; LC 1.7 min. (50/80).

82		33	NMR δ_H (400 MHz, DMSO) 3.62 – 3.66 (2H, m), 4.59 (2H, d, *J* 6.0Hz), 5.00 – 5.17 (5H, m), 5.76 – 5.85 (1H, m), 6.71 – 6.72 (1H, m), 6.93 (2H, s), 7.25 – 7.28 (2H, m), 7.30 (1H, dd, *J* 3.5Hz, 1.0Hz), 7.42 (1H, s), 7.57 (1H, t, *J* 5.5Hz), 7.80 (1H, t, *J* 7.5Hz), 7.94 – 7.95 (1H, m), 9.01 (1H, t, *J* 6.0Hz); LC 1.4 min. (50/80).
83	J	28	Mp 131.0 - 131.1 °C; IR ν_{max} (DR)/cm^{-1} 3367, 3196, 2940, 1636, 1522, 1224, 1027 and 746; NMR δ_H (400 MHz, DMSO) 8.42 (1H, t, *J* 6.0 Hz), 7.94-7.93 (1H, m), 7.38 (1H, s), 7.31-7.15 (6H, m), 6.86 (2H, br s), 6.71 (1H, dd, *J* 3.0, 1.5 Hz), 3.32 (2H, t, *J* 7.0 Hz), 2.62 (2H, t, *J* 7.5 Hz) and 1.88-1 .79 (2H, m); M/Z 323 $(M+H)^+$; LC 4.1 min. (50/80).
84		35	IR ν_{max} (DR)/cm^{-1} 3240, 1666, 1458, 1310, 1028 and 765; NMR δ_H (400 MHz, DMSO) 8.92 (1H, t, *J* 6.0 Hz), 7.97-7.94 (1H, m), 7.44 (1H, s), 7.36-7.20 (4H, m), 6.72 (1H, dd, *J* 3.5, 1.5 Hz), 4.46 (2H, d, *J* 6.5 Hz) and 2.32 (3H, s); M/Z 324 $(M+H)^+$; LC 1.2 min. (50/80).
85		57	Mp 151.6 – 155.7 °C; NMR δ_H (400 MHz, DMSO) 0.84 (3H, t, *J* 7.0Hz), 1.40 – 1.47 (2H, m), 2.97 (2H, q, *J* 6.5Hz), 4.60 (2H, d, *J* 5.5Hz), 5.09 (2H, s), 6.71 – 6.72 (1H, m), 6.93 (2H, s), 7.24 – 7.27 (2H, m), 7.30 (1H, dd, *J* 3.5Hz, 1.0Hz), 7.36 (1H, t, *J* 8.0Hz), 7.42 (1H, s), 7.80 (1H, t, *J* 8.0Hz), 7.94 – 7.95 (1H, m), 9.01 (1H, t, *J* 6.0Hz); LC 1.6 min. (50/80).
86		43	NMR δ_H (400 MHz, DMSO) 1.24 (9H, s), 4.59 (2H, d, *J* 6.0Hz), 5.05 (2H, s), 6.71 – 6.72 (1H, m), 6.93 (2H, s), 7.13 (1H, s), 7.25 (1H, d, *J* 3.0Hz), 7.27 (1H, d, *J* 2.5Hz), 7.30 – 7.31 (1H, m), 7.42 (1H, s), 7.80 (1H, t, *J* 8.0Hz), 7.94 – 7.94 (1H, m), 9.00 (1H, t, *J* 6.0Hz); LC 2.3 min. (50/80).
87	J	36	M/Z 309 $(M+H)^+$; LC 1.4 min. (50/80).
88	J	11	Mp 191.9 - 1 92.0 °C; NMR δ_H (400 MHz, DMSO) 8.94 (1H, t, *J* 5.5 Hz), 8.50 (2H, d, *J* 8.5 Hz), 7.93 (1H, s), 7.41 (1H, s), 7.29 (1H, d, *J* 3.5 Hz), 6.89 (2H, br s), 6.72-6.69 (1H, m), 4.63 (2H, d, *J* 5.5 Hz) and 2.48 (3H, s); M/Z 311 $(M+H)^+$; LC 4.8 min. (20/50).
89	J	38	Mp 178.1 - 1 78.7 °C; IR ν_{max} (DR)/cm^{-1} 3331, 3181, 2926, 1541, 1228, 1011 and 885; NMR δ_H (400 MHz, DMSO) 8.38 (1H, d, *J* 9.0 Hz), 7.94 (1H, t, *J* 1.0 Hz), 7.46 (1H, br s), 7.30 (1H, dd, *J* 3.5, 1.0 Hz), 7.22-7.12 (4H, m), 6.91 (2H, br s), 6.71 (1H, dd, *J* 1.5, 2.0 Hz), 5.21-5.14 (1H, m), 2.87-2.69 (2H, m), 2.06-1 .96 (1H, m) and 1.92-1 .77 (3H, m); M/Z 355 $(M+H)^+$; LC 5.1 min. (50/80).
90	J	58	Mp 220.0 - 221.3 °C; IR ν_{max} (DR)/cm^{-1} 3332, 3198, 1634, 1520, 1238 and 742; NMR δ_H (400 MHz, DMSO) 8.41 (1H, d, *J* 7.5 Hz), 7.95-7.91 (1H, m), 7.40 (1H, s), 7.28 (1H, d, *J* 4.0 Hz), 7.27-7.14 (2H, m), 6.88 (2H, br s), 6.70 (1H, dd, *J* 3.5, 2.0 Hz), 4.75-4.64 (1H, m), 3.26 (2H, dd, *J* 16, 7.0 Hz) and 2.95 (2H, dd, *J* 16, 6.0 Hz); M/Z 321 $(M+H)^+$; LC 4.0 min. (50/80).

91			LC 3.4 min. (20/50).
92			LC 1.1 min. (20/50).
93	J	87	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 4.54 (2H, d, *J* 6.0 Hz), 6.71 (1H, m), 6.89 (2H, br s), 7.30 (1H, m), 7.35 – 7.38 (2H, m), 7.42 (1H, s), 7.64 (1H, m), 7.94 (1H, m) and 8.83 (1H, t, *J* 6.0 Hz); M/Z 373 $(M+H)^+$ and 375 $(M+H)^+$; LC 4.4 min. (50/80).
94	J	78	Mp 178.1 – 179.3 °C, M/Z 374 $(M+H)^+$; LC 1.9 min. (50/80).
95		22	Mp 223.8 – 223.9 °C; NMR δ_H (400 MHz, DMSO) 4.36 (2H, d, *J* 5.5Hz), 5.94 (2H, s), 6.34 (1H, d, *J* 7.5Hz), 6.45 (1H, d, *J* 7.0Hz), 6.70 – 6.71 (1H, m), 6.93 (2H, s), 7.29 – 7.30 (1H, m), 7.34 (1H, t, *J* 7.5Hz), 7.42 (1H, s), 7.93 – 7.94 (1H, m), 8.87 (1H, t, *J* 5.5Hz); LC 0.9 min. (50/80).
96	J	73	Mp 248.2 – 249.0 °C; M/Z 313 $(M+H)^+$; LC 3.7 min. (50/80).
97			LC 4.6 min. (20/50).
98			LC 5.0 min. (20/50).
99		20	M/Z 459 $(M+H)^+$; LC 3.2 min. (50/80).
100		17	M/Z 437 $(M+H)^+$; LC 2.7 min. (50/80).
101		36	M/Z 453 $(M+H)^+$; LC 4.9 min. (50/80).

102	J	73	Mp 203.0 – 203.1 °C, M/Z 353 $(M+H)^+$; LC 2.7 min. (50/80).
103	K	64	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 3.70 (3H, s), 5.66 (1H, m), 6.71 (1H, dd, *J* 1.8, 3.5 Hz), 7.07 (2H, br s), 7.30 (1H, d, *J* 3.5 Hz), 7.37 – 7.46 (6H, m), 7.94 (1H, m) and 8.75 (1H, d, J 7.3 Hz); M/Z 353 $(M+H)^+$; LC 2.5 min. (50/80).
104	K	39	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 3.70 (3H, s), 5.66 (1H, m), 6.71 (1H, dd, *J* 1.8, 3.5 Hz), 7.07 (2H, br s), 7.30 (1H, d, *J* 3.5 Hz), 7.37 – 7.46 (6H, m), 7.94 (1H, m) and 8.75 (1H, d, J 7.3 Hz); M/Z 353 $(M+H)^+$; LC 2.8 min. (50/80).
105	J	17	M/Z 363 $(M+H)^+$, 365 $(M+H)^+$; LC 4.6 min. (50/80).
106	J	65	NMR δ_H (400 MHz, DMSO) 9.06(1H,t,J 6.5Hz),7.92(1H, d, J 1.0Hz), 7.80 (1H,t, J 7.5Hz), 7.32-7.27(2H, m), 7.15(1H, dd, J 1.0Hz, J 3.5Hz) 6.70 (1H, dd, J 1.5Hz, J 3.5Hz), 6.61 (2H, br s), 4.51(2H, d, J 6.0Hz), 4.49(2H,s), 3.37 (3H, s) and 2.33 (3H,s); LC: RT 5.06 min (20:50); M/Z 354 $(M+H)^+$; LC 5.1 min. (20/50).
107	J	59	IR ν_{max} (DR)/cm^{-1} ; NMR δ_H (400 MHz, DMSO) 3.57 (3H, s), 4.69 (2H, s), 4.77 (2H, d, *J* 6.0 Hz), 7.40 (2H, br s), 7.57 (1H, d, *J* 8.0 Hz), 7.63 (1H, d, *J* 7.6 Hz), 7.77 (1H, s), 8.02 (1H, d, *J* 3.2 Hz), 8.10 (1H, d, *J* 2.8 Hz), 8.16 (1H,m) and 9.20 (1H, t, *J* 6.0 Hz); M/Z 357 $(M+H)^+$; LC 0.9 min. (50/80).
108	J	46	Mp 229.6 - 231.7 °C; IR ν_{max} (DR)/cm^{-1} 3470, 3358, 1672, 1634, 1514 and 782; NMR δ_H (400 MHz, DMSO) 9.08 (1H, t, *J* 5.0 Hz), 8.42 (1H, d, *J* 4.5 Hz), 8.10 (1H, d, *J* 3.0 Hz), 8.01 (1H, d, *J* 3.0 Hz), 7.81 (1H, s), 7.64 (1H, d, *J* 6.5 Hz), 7.30-7.21 (3H, m), 4.64 (2H, d, *J* 5.0 Hz) and 2.33 (3H, s); M/Z 327 $(M+H)^+$; LC 1.3 min. (50/80).
109	J	17	Mp 144.1 - 144.3 °C; IR ν_{max} (DR)/cm^{-1} 3471, 3343, 1673, 1232, 866, 780 and 616; NMR δ_H (400 MHz, DMSO) 9.02 (1H, t, *J* 6.0 Hz), 8.11 (1H, d, *J* 3.0 Hz), 8.02 (1H, d, *J* 3.0 Hz), 7.77 (1H, s), 7.67 (1H, t, *J* 7.5 Hz), 7.27-7.10 (4H, m), 4.58 (2H, d, *J* 6.0 Hz), 2.71 (2H, d, *J* 7.5 Hz), 1.69 (2H, m), 0.92 (3H, t, *J* 7.5 Hz); M/Z 355 $(M+H)^+$; LC 2.5 min. (50/80).
110	J	40	M/Z 377 $(M+H)^+$; LC 5.3 min. (50/80).
111	J	40	M/Z 310 $(M+H)^+$; LC 1.2 min. (50/80).

112	J	19	M/Z 312 $(M+H)^+$; LC 2.3 min. (50/80).
113	J	18	M/Z 354 $(M+H)^+$
114		38	M/Z 439 $(M+H)^+$; LC 3.4 min. (50/80).
115		10	M/Z 453 $(M+H)^+$; LC 1.6 min. (50/80).
116		54	M/Z 388 $(M+H)^+$, 390 $(M+H)^+$; LC 6.5 min. (50/80).
117		82	M/Z 432$(M+H)^+$, 434 $(M+H)^+$; LC 1.1 min. (50/80).
118	J	67	M/Z 455$(M+H)^+$, 457 $(M+H)^+$; LC 4.4 min. (50/80).
119	J	29	M/Z 323 $(M+H)^+$; LC
120	J	44	M/Z 323 $(M+H)^+$; LC
121	J	53	M/Z 323 $(M+H)^+$; LC
122	J	23	M/Z 344 $(M+H)^+$; LC

123	J	60	M/Z 344 $(M+H)^+$; LC
124	J	9	M/Z 310 $(M+H)^+$; LC
125	J	21	M/Z 310 $(M+H)^+$; LC
126	J	60	M/Z 339 $(M+H)^+$; LC
127	J	57	M/Z 339 $(M+H)^+$; LC
128	J	52	M/Z 327 $(M+H)^+$; LC
129	J	34	M/Z 327 $(M+H)^+$; LC
130	J		NMR δ_H (400 MHz, DMSO) 4.14 (2H, s), 4.53 (2H, d, *J* 6.0 Hz), 6.70 – 6.71 (1H, m), 6.86 (2H, s), 7.23 – 7.30 (5H, m), 7.35 – 7.40 (7H, m), 7.45 – 7.48 (6H, m), 7.61 (1H, d, *J* 7.5 Hz), 7.90 (1H, t, *J* 7.5 Hz), 7.93 – 7.94 (1H, m), 8.91 (1H, t, *J* 6.0Hz); LC 7.8 min. (20/50).
131	J		NMR δ_H (400 MHz, DMSO) 8.56-8.52 (1H, m), 7.78 (1H, m), 7.65-7.64 (1H, m), 7.25 (1H, d, J 4.0), 7.07 (1H, d, J 1.0), 7.05 (1H, d, J 1.0), 6.61-6.59 (1H, m), 5.39 (2H, s), 5.15 (2H, s), 4.81 (2H, d, J 5.0), 3.56-3.52 (2H, m), 0.94-0.89 (2H, m), 0.00 (9H, s); M/Z 415 $(M+H)^+$.
132	J		NMR δ_H (400 MHz, DMSO) 0.10 (6H, s), 0.92 (9H, s), 2.39 (3H, s), 4.57 (2H, d, *J* 6.0 Hz), 4.57 (2H, d, *J* 6.0 Hz), 4.76 (2H, s), 6.34 – 6.35 (1H, m), 6.87 (2H, s), 7.20 – 7.22 (2H, m), 7.33 (1H, d, *J* 7.5 Hz), 7.36 (1H, s), 7.80 (1H, t, *J* 7.5 Hz), 8.93 (1H, t, *J* 6.0 Hz); M/Z 454 $(M+H)^+$
133	AD	49	NMR δ_H (400 MHz, DMSO) 2.39 (3H, s), 4.56 – 4.57 (4H, m), 6.33 – 6.34 (1H, m), 6.89 (2H, s), 7.18 (1H, d, *J* 7.5 Hz), 7.21 (1H, d, *J* 3.0 Hz), 7.36 – 7.38 (2H, m), 7.76 (1H, t, *J* 8.0 Hz), 8.96 (1H, t, *J* 6.0 Hz); M/Z 340 $(M+H)^+$.

Adenosine Receptor Binding

Binding Affinities at hA_{2A} Receptors

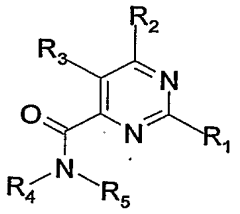
The compounds were examined in an assay measuring *in vitro* binding to human adenosine A_{2A} receptors by determining the displacement of the adenosine A_{2A} receptor selective radioligand [^{3}H]-CGS 21680 using standard techniques.

The following compounds have a K_i of <50 nM in this assay demonstrating potent binding affinity for the human adenosine A_{2A} receptor.

Examples 1, 3, 6, 7, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20,23, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 35, 37, 38, 41, 42, 45, 46, 48, 49, 50, 51, 52, 53, 54, 55, 57, 58, 59, 60, 61, 62, 64, 66, 69, 73, 74, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 90, 91, 92, 93, 94, 95, 98, 99, 100, 101, 102, 103, 104, 105, 106, 109, 110, 111, 112, 113, 114, 115, 118, 119, 120, 122, 123, 125, 126, 127, 128 and 129.

CLAIMS

1. The use of a compound of formula (1):



(I)

wherein

R_1 is selected from H, alkyl, NR_6R_7, OR_8, SR_9 and halogen;

R_2 is selected from aryl and heteroaryl attached via a carbon atom;

R_3 is selected from H, alkyl, halogen, OH and OR_{10};

R_4 is selected from H, alkyl, aryl and heteroaryl,

R_5 is selected from H and alkyl;

or R_4 and R_5 together form a 5 or 6-membered heterocyclic ring;

R_6 and R_7 are independently selected from H and alkyl; and

R_8, R_9 and R_{10} are independently selected from alkyl;

and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the blocking of purine receptors is beneficial.

2. The use of claim 1 wherein R_1 is selected from NR_6R_7, OR_8, SR_9 and halogen.

3. The use of claim 1 wherein R_1 is selected from NR_6R_7, OR_8 and SR_9.

4. The use of claim 1 wherein R_1 is selected from NR_6R_7 and at least one of R_6 and R_7 is selected from H.

5. The use of claim 1 wherein R_1 is selected from NH_2.

6. A use according to any preceding claim wherein R_2 is selected from monocyclic aryl and heteroaryl attached via a carbon atom.

7. A use according to any preceding claim wherein R_2 is not ortho-substituted.

8. A use according to any preceding claim wherein R_2 is not ortho,ortho-disubstituted.

9. A use according to any preceding claim wherein R_2 is selected from heteroaryl.

10. A use according to any preceding claim wherein R_2 is selected from heteroaryl containing one or more heteroatom(s) selected from O, S and N atoms.

11. A use according to any preceding claim wherein R_2 is selected from heteroaryl containing one or more heteroatom(s) selected from O, S and N atoms wherein said heteroatom(s) are adjacent the carbon atom which is attached to the pyrimidine ring.

12. A use according to any preceding claim wherein R_2 is selected from furyl, thienyl, thiazolyl, oxazolyl, imidazolyl and pyridyl.

13. A use according to any of claims 1 to 8 wherein R_2 is phenyl.

14. A use according to any preceding claim wherein R_3 is selected from H, alkyl and halogen.

15. A use according to any of claims 1 to 14 wherein R_4 is selected from alkyl, aryl and heteroaryl.

16. A use according to any of claims 1 to 14 wherein R_4 is selected from H, alkyl and heteroaryl or forms a heterocyclic ring with R_5.

17. A use according to any of claims 1 to 14 wherein R_4 is selected from H and heteroaryl or forms a heterocyclic ring with R_5.

18. A use according to any of claims 1 to 14 wherein R_4 is selected from heteroaryl or forms a heterocyclic ring with R_5.

19. A use according to any of claims 1 to 14 wherein R_4 is selected from heteroaryl.

20. A use according to any preceding claim wherein R_5 is selected from H or together with R_4 forms a 5 or 6-membered heterocyclic ring.

21. A use according to any preceding claim wherein R_5 is H.

22. A method of treating or preventing a disorder in which the blocking of purine receptors is beneficial, the method comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as set out in any of claims 1 to 21 or a pharmaceutically acceptable salt or prodrug thereof.

23. A compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof, *per se*, as set out in any of claims 1 to 21, other than compounds wherein R_2 is selected from pyrazolopyridines.

24. For use in therapy a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, as set out in any of claims 1 to 21, other than compounds wherein R_2 is selected from pyrazolopyridines.

25. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof as set out in any of claims 1 to 21 other than compounds wherein R_2 is selected from pyrazolopyridines in combination with a pharmaceutically acceptable carrier or excipients.

26. A use or method according to any of claims 1 to 22 wherein said receptors are adenosine receptors.

27. A use or method according to any of claims 1 to 22 wherein said receptors are adenosine A_{2A} receptors.

28. A use or method according to any of claims 1 to 22 wherein the disorders are selected from movement disorders; acute and chronic pain; affective disorders; central and

peripheral nervous system degenerative disorders; schizophrenia; cognitive and memory impairment disorders; attention disorders; central nervous system injury; cerebral ischaemia; myocardial ischaemia; muscle ischaemia; sleep disorders; eye disorders; cardiovascular disorders; and diabetes

29. A use or method according to claim 28 wherein the movement disorder is selected from Parkinson's disease, progressive supernuclear palsy, Huntingtons disease, multiple system atrophy, corticobasal degeneration, Wilsons disease, Hallerrorden-Spatz disease, progressive pallidal atrophy, Dopa-responsive dystonia-Parkinsonism and spasticity.

30. A use or method according to claim 28 wherein the disorder is selected from neuropathic pain, cancer pain, trigeminal neuralgia, migraine, cephalic pain, primary and secondary hyperalgesia, inflammatory pain, nociceptive pain, tabes dorsalis, phantom limb pain, spinal cord injury pain, central pain, post-herpetic pain and HIV pain.

31. A use or method according to claim 28 wherein said affective disorder is selected from bipolar disorder, seasonal affective disorder, depression, manic depression, atypical depression and monodepressive disease.

32. A use or method according to claim 28 wherein said central and peripheral nervous system degenerative disorder is selected from corticobasal degeneration, demyelinating disease, Freidrich's ataxia, motoneurone disease, multiple system atrophy, myelopathy, radiculopathy, peripheral neuropathy, systemic lupus erythamatosis, granulomatous disease, olivo-ponto-cerebellar atrophy, progressive pallidal atrophy, progressive supranuclear palsy and spasticity.

33. A use or method according to claim 28 wherein said cognitive and/or memory impairment disorder is selected from dementia, Alzheimers Disease, Frontotemporal dementia, multi-infarct dementia, AIDS dementia, dementia associated with Huntingtons Disease, Lewy body dementia, senile dementia, age-related memory impairment, cognitive impairment associated with dementia, Korsakoff syndrome, dementia pugilans;

34. A use or method according to claim 28 wherein attention disorder is selected from attention-deficit hyperactivity disorder (ADHD), attention deficit disorder, minimal brain dysfunction, brain-injured child syndrome, hyperkinetic reaction childhood and hyperactive child syndrome.

35. A use or method according to claim 28 wherein said central nervous system injury is selected from traumatic brain injury, surgical trauma, raised intracranial pressure, cerebral oedema, hydrocephalus and spinal cord injury.

36. A use or method according to claim 28 wherein said cerebral ischaemia is transient ischaemic attack, stroke, subarachnoid haemorrhage, cerebral vasospasm, peri-natal asphyxia, drowning, cardiac arrest or subdural haematoma.

37. A use or method according to claim 28 wherein the sleep disorder is selected from hypersomnia, narcolepsy and restless legs syndrome.

38. A use or method according to claim 28 wherein the eye disorder is selected from retinal ischaemia-reperfusion injury and diabetic neuropathy.

39. Use of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof according to any of claims 1 to 21 in the manufacture of a medicament for neuroprotection in a subject.

40. A method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as set out in any of claims 1 to 21 or a pharmaceutically acceptable salt or prodrug thereof.